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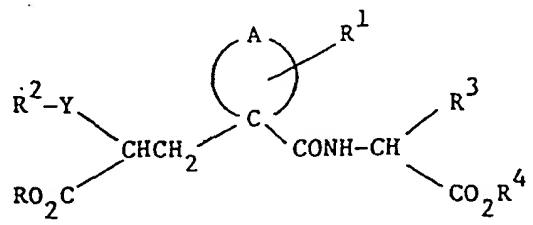

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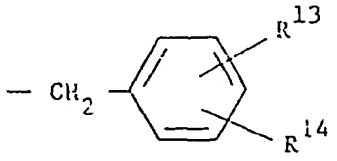

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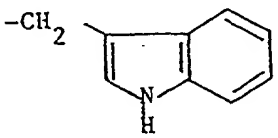

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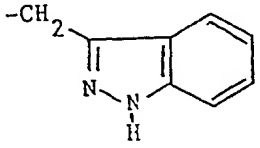

(IV)

(57) Abstract

Compounds of formula (I), wherein A completes a 5 or 6 membered carbocyclic ring which may be saturated or monounsaturated; Y is an alkylene group of from 1 to 9 carbon atoms; R^1 is H or $(C_1$-$C_4)$alkyl; R and R^4 are H, $(C_1$-$C_6)$alkyl, $(C_3$-$C_7)$cycloalkyl, benzyl, or an alternative biolabile ester-forming group; R^2 is defined to include a range of substituent groups including $(C_1$-$C_6)$alkoxy, $(C_1$-$C_4)$alkoxy-$(C_1$-$C_6)$alkoxy and various substituted-alkyl, amino, substituted amino, aryl and heterocyclyl substituents linked directly or by O, $S(O)_n$, NR^6, CO or $CONR^6$ wherein R^6 is H, $(C_1$-$C_4)$alkyl or aryl$(C_1$-$C_4)$alkyl and n is 0, 1 or 2; R^3 is a group of formula (II), wherein R^{13} is H, halo, 4-OH, 4-$(C_1$-C_6 alkoxy), 4-$(C_3$-C_7 cycloalkoxy), 4-$(C_2$-C_6 alkenyloxy), 4-[$(C_1$-C_6 alkoxy)carbonyloxy], 4-[$(C_3$-C_7 cycloalkyloxy)carbonyloxy], or 3-$(C_1$-C_4 alkyl)SO_2NH-; and R^{14} is H, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, $(C_2$-$C_6)$alkanoyl or halo; or R^3 is a group of formulae (III) or (IV), wherein said groups may optionally be substituted in the fused benzene ring by $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, OH, halo or CF_3; or are atriopeptidase inhibitors or utility in the treatment of hypertension and heart failure.

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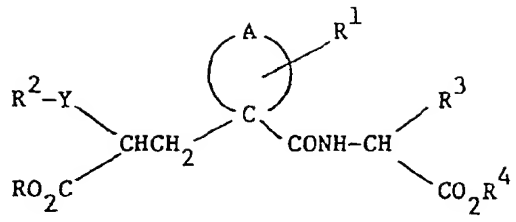
"Cycloalkyl-substituted Glutaramide Antihypertensive Agents"

This invention relates to a series of cycloalkyl-substituted glutaramide derivatives which are antihypertensive agents having utility in the treatment of various cardiovascular disorders, including hypertension and heart failure.

According to the specification of our European patent application 274234, we disclose certain cycloalkyl-substituted glutaramide derivatives which are inhibitors of the zinc dependent neutral endopeptidase E.C.3.4.24.11 (atriopeptidase) and which are thereby able to potentiate the biological effects of atrial natriuretic factor and in particular, are natriuretic, antihypertensive and diuretic agents of value in the treatment of various cardiovascular disorders. In our European patent application no. 89308740.3 we describe compounds which are inhibitors of the enzyme E.C.3.4.24.11 and, in addition, they are also able to inhibit angiotensin converting enzyme (ACE), a further enzyme which is involved in the control of blood pressure. The compounds thus have a dual pharmacological action through inhibiting two key enzymes involved in blood pressure control which makes them particularly useful in the treatment of various forms of hypertension and associated cardiovascular disorders, e.g. congestive heart failure and glaucoma.

According to the present invention there are provided further related compounds having activity as atriopeptidase and ACE inhibitors of the formula:



(I)

wherein:

A completes a 5 or 6 membered carbocyclic ring which may be saturated or monounsaturated;

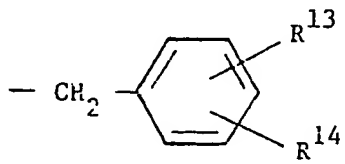
Y is an alkylene group of from 1 to 9 carbon atoms which may be straight or branched chain;

R^1 is H or (C_1-C_4)alkyl;

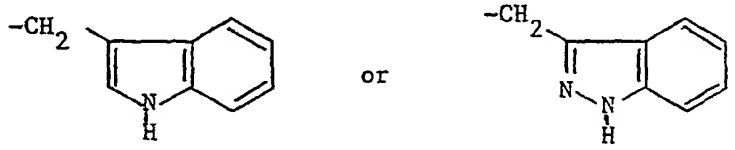
R and R^4 are each independently H, (C_1-C_6)alkyl, (C_3-C_7) cycloalkyl, benzyl, or an alternative biolabile ester-forming group;

R^2 is hydroxy, (C_1-C_6)alkoxy, hydroxy(C_2-C_6)alkoxy, (C_1-C_6)alkyl-$S(O)_n$-, (C_1-C_4)alkoxy(C_1-C_6)alkoxy, (C_1-C_4)alkyl-$S(O)_n$-(C_1-C_6)-alkoxy, (C_1-C_4)alkoxy(C_2-C_6)alkenyloxy, N_3, $(R^5)_2N$, $(R^5)_2N$-(C_1-C_6)alkoxy, $(R^5)_2N$-(C_2-C_6)alkenyloxy, heterocyclyl-Z-, heterocyclyl(C_1-C_4)alkyl-Z-, aryl-Z- or aryl(C_1-C_4)alkyl-Z, wherein Z is O, $S(O)_n$ or NR^6 and R^6 is H, (C_1-C_4)alkyl or aryl(C_1-C_4)alkyl;
or R^2 is a group of the formula R^7R^8CH- in which case Y may also be a direct link and wherein R^7 is $(R^5)_2N(C_1-C_4)$alkyl, (C_1-C_4)-alkoxy(C_2-C_4)alkylaminomethyl, heterocyclyl(C_1-C_4)alkyl or aryl and R^8 is (C_1-C_6) alkoxy, (C_1-C_4)alkoxy(C_2-C_6)alkoxy, hydroxy(C_2-C_6)alkoxy or hydroxy(C_1-C_6)alkyl;
or R^2 is a group of the formula R^9CO- wherein R^9 is a 1-piperidine or 1-piperazine group, either of which may optionally be substituted by OH, =O, (C_1-C_4)alkyl or $N(R^5)_2$;
or R^2 is a group of the formula $R^{10}CONR^6$- wherein R^6 is as previously defined, and R^{10} is $(R^6)_2N$, (C_1-C_4)alkoxy(C_2-C_4)alkyl, $R^{11}R^{12}CH$-, or substituted phenyl wherein the substituent is $(R^5)_2N$-(C_1-C_4)alkyl, (C_1-C_4)alkyl-$S(O)_n$- or (C_1-C_4)alkyl-$S(O)_n$-(C_1-C_4)alkyl;

R^3 is a group of the formula:



wherein R^{13} is H, halo, 4-OH, 4-(C_1-C_6 alkoxy), 4-(C_3-C_7 cycloalkoxy), 4-(C_2-C_6 alkenyloxy), 4-[(C_1-C_6 alkoxy)carbonyloxy], 4-[(C_3-C_7 cycloalkoxy)carbonyloxy], or 3-(C_1-C_4 alkyl)SO_2NH-; and R^{14} is H, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_2-C_6) alkanoyl or halo; or R^3 is a group of the formula:



wherein said groups may optionally be substituted in the fused benzene ring by (C_1-C_4)alkyl, (C_1-C_4)alkoxy, OH, halo or CF_3;

each R^5 is H, (C_1-C_6)alkyl, aryl(C_1-C_6)alkyl or the two groups R^5 are taken together to form, with the nitrogen to which they are attached, a pyrrolidinyl, piperidino, morpholino, piperazinyl or N-(C_1-C_4)alkyl-piperazinyl group;

R^{11} is (C_1-C_4)alkyl-S(O)$_n$NH- or (C_1-C_4)alkanoylamino and R^{12} is (C_1-C_4)alkyl-S(O)$_n$(C_1-C_4)alkyl or morpholinomethyl or R^{11} and R^{12} are both morpholinomethyl or (C_1-C_4)alkoxy(C_1-C_4)alkoxy(C_1-C_4)-alkyl;

n is 0, 1 or 2

and pharmaceutically acceptable salts thereof and bioprecursors therefor.

In the above definition, unless otherwise indicated, alkyl groups having three or more carbon atoms may be straight or branched-chain. The term aryl as used herein means an aromatic hydrocarbon group such as phenyl or naphthyl which may optionally be substituted with, for example, one or more OH, CN, CF_3, (C_1-C_4) alkyl, (C_1-C_4)alkoxy, halo, carbamoyl, aminosulphonyl, amino, mono or di(C_1-C_4 alkyl)amino, (C_1-C_4 alkanoyl)amino, amino(C_1-C_4)alkyl, di(C_1-C_4 alkyl)amino(C_1-C_4)alkyl, or (C_1-C_4) alkyl-$S(O)_n$-(C_1-C_4)alkyl groups. Halo means fluoro, chloro, bromo or iodo.

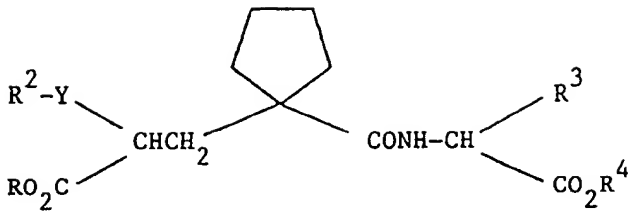
The term heterocyclyl means a 5 or 6 membered nitrogen, oxygen or sulphur containing heterocyclic group which, unless otherwise stated, may be saturated or unsaturated and which may optionally include a further oxygen or one to three nitrogen atoms in the ring and which may optionally be benzofused or substituted with for example, one or more halo, (C_1-C_4)alkyl, hydroxy, carbamoyl, benzyl, oxo, amino or mono or di-(C_1-C_4 alkyl)amino or (C_1-C_4 alkanoyl)amino groups. Particular examples of heterocycles include pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, piperidino, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, tetrahydropyranyl, dioxanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, indolyl, isoindolinyl, quinolyl, quinoxalinyl, quinazolinyl and benzimidazolyl, each being optionally substituted as previously defined.

The compounds of formula (I) may contain several asymmetric centres and thus they can exist as enantiomers and diastereomers. The invention includes both the separated individual isomers as well as mixtures of isomers.

The pharmaceutically acceptable salts of the compounds of formula (I) containing an acidic centre are those formed with bases which form non-toxic salts. Examples include the alkali or alkaline earth metal salts such as the sodium, potassium or calcium salts or salts with amines such as diethylamine. Compounds having a basic centre can also form acid addition salts with pharmaceutically acceptable acids. Examples include the hydrochloride, hydrobromide, sulphate or bisulphate, phosphate or hydrogen phosphate, acetate, citrate, fumarate, gluconate, lactate, maleate, succinate, tartrate tosylate and lauryl sulphate salts.

The term bioprecursor in the above definition means a pharmaceutically acceptable biologically degradable derivative of the compound of formula (I) which, upon administration to an animal or human being, is converted in the body to produce a compound of the formula (I). Examples include biolabile ester derivatives and amide or amino acid derivatives of the compounds of formula I.

A preferred group of compounds of the formula (I) are those wherein A is $(CH_2)_4$ and R^1 is H, i.e. compounds of the formula (II) wherein R, R^2, R^3 and R^4 are as previously defined for formula (I):



(II)

Also preferred are those compounds of formulae (I) and (II) wherein R and R^4 are both H (diacids) as well as biolabile mono and di-ester derivatives thereof wherein one or both of R and R^4 is a biolabile ester-forming group.

The term biolabile ester-forming group is well understood in the art as meaning a group which provides an ester which can be readily cleaved in the body to liberate the corresponding diacid of formula (I) wherein R and R^4 are both H. A number of such ester groups are well known, for example in the penicillin area or in the case of the ACE-inhibitor antihypertensive agents.

In the case of the compounds of formulae (I) and (II) such biolabile pro-drug esters are particularly advantageous in providing compounds of the formula (I) suitable for oral administration. The suitability of any particular ester-forming group can be assessed by conventional animal or in vitro enzyme hydrolysis studies. Thus, desirably for optimum effect, the ester should only be hydrolysed after absorption, accordingly, the ester should be resistant to hydrolysis by digestive enzymes before

absorption but should be readily hydrolyzed by, for example, gut-wall, plasma or liver enzymes. In this way the active diacid is released into the bloodstream following oral absorption.

In addition to lower alkyl esters (particularly ethyl) and benzyl esters, alternative biolabile esters include alkanoyloxyalkyl esters, including alkyl, cycloalkyl and aryl substituted derivatives thereof, aroyloxyalkyl esters, arylesters, aralkylesters, haloalkyl esters and hydroxyalkyl esters including ketal derivatives thereof, wherein said alkanoyl or alkyl groups have from 1 to 18 carbon atoms and are branched or straight chain and said aryl groups are phenyl, naphthyl or indanyl optionally substituted with one or more (C_1-C_{14})alkyl, (C_1-C_{14})alkoxy or (C_2-C_{14})alkoxycarbonyl groups or halo atoms.

Thus examples of R and R^4 when they are biolabile ester groups include ethyl, indanyl, isopropyl, n-butyl, sec-butyl, t-butyl, cyclohexyl, benzyl, phenethyl, phenpropyl, acetonyl, glyceryl, pivaloyloxymethyl, 5-(4-methyl-1,3-dioxolene-2-onyl)methyl, cyclohexylmethyl, cyclohexylcarboxyethyl, cyclohexylacetoxyethyl, propionyloxyisobutyl, hexanoyloxyethyl, pentanoyloxyethyl, acetoxyethyl, acetoxybenzyl, pentanoyloxybenzyl, cyclohexyloxycarbonyloxyethyl, butyloxycarbonyloxyethyl, isobutyloxycarbonylethyl and ethoxycarbonyloxyethyl.

In one preferred aspect of the invention, the group R^3 is 4-hydroxybenzyl and the carbon atom to which it is attached is of (S) stereochemistry; the group $NHCH(R^3)CO_2R^4$ being derived from L-tyrosine. Also preferred are compounds wherein R^3 is 4-methoxybenzyl.

The substituent R^2Y is preferably (C_1-C_6)alkoxy(C_1-C_4)alkyl or (C_1-C_4)alkoxy(C_1-C_6)alkoxy(C_1-C_4)alkyl. Thus particular and preferred examples include ethoxyethyl and 2-(methoxyethoxy)-propyl.

Also preferred are compounds where R^2Y is amino(C_4-C_9)alkyl. A particular and preferred example of this type is 8-amino-octyl.

In a further group of preferred compounds Y is CH_2 and R^2 is of formula $R^{10}CONR^6-$ wherein R^6 is H. Particularly preferred are examples wherein R^{10} is substituted phenyl particularly when said substituent is H_2NCH_2-, $(CH_3)_2NCH_2-$ or $CH_3S(O)_nCH_2-$ (wherein n is 0, 1 or 2).

Thus particular and preferred compounds of the invention include-:

N-[1-{2(S)-carboxy-4-(2-methoxyethoxy)pentyl}-1-cyclopentane-carbonyl]-(S)-tyrosine,

N-[1-(2(S)-carboxy-4-ethoxybutyl)-1-cyclopentanecarbonyl]-(S)-tyrosine,

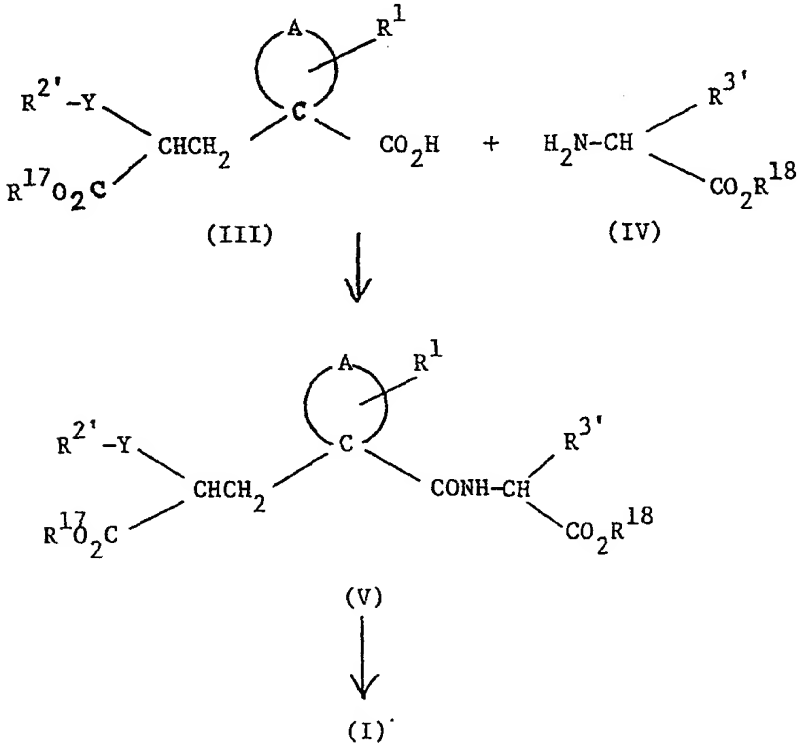
N-[1-(2(R,S)-carboxy-10-aminodecyl)-1-cyclopentanecarbonyl]-(S)-tyrosine and

N-[1-{2(S)-carboxy-3-(4-aminomethylbenzamido)propyl}-1-cyclo-pentanecarbonyl]-(S)-tyrosine.

The compounds of formula (I) are prepared by a number of different processes:

a) One procedure involves the synthesis of a partially protected cycloalkyl-substituted glutaric acid derivative which is coupled to an amino acid ester derivative to give the desired glutaramide. Any reactive groups in R^2 and R^3 may require protection during the coupling step and such protecting groups are removed in the final stage of the process.

The synthetic route is illustrated in the following reaction scheme wherein A, Y and R^1 are as previously defined, $R^{2'}$ and $R^{3'}$ are as defined for R^2 and R^3 with any reactive groups therein protected if necessary and R^{17} and R^{18} are as defined for R and R^4 excluding H, or they are conventional carboxylic acid protecting groups:



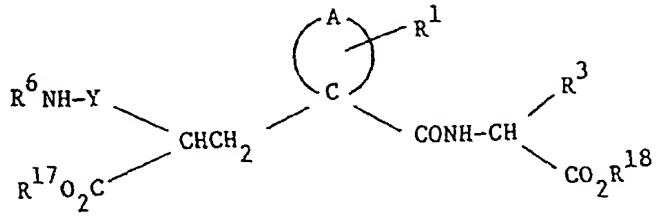
The reaction of the compounds of formula (III) and (IV) is achieved using conventional amide coupling techniques. Thus in one process the reaction is achieved with the reactants dissolved in an organic solvent, e.g. dichloromethane, using a diimide condensing agent, for example 1-ethyl-3-(dimethylaminopropyl)-carbodiimide, or N,N'-dicyclohexylcarbodiimide, advantageously in the presence of 1-hydroxybenzotriazole and an organic base such as N-methylmorpholine. The reaction is generally complete after a period of from 12 to 24 hours at room temperature and the product is then isolated by conventional procedures, i.e. by washing with water or filtration to remove the urea biproduct and evaporation of the solvent. The product may be further purified by crystallisation or chromatography, if necessary.

The compounds of formula (V) include compounds of formula (I) wherein R and R^4 are C_1-C_6 alkyl or benzyl.

The diesters of formula (V) are subsequently reacted to give the monoester or diacid derivatives of formula (I) wherein one or both of R and R^4 are H. The conditions used will depend on the precise nature of the groups R^{17} and R^{18} present in the compound of formula (V) and a number of variations are possible. Thus for example when both of R^{17} and R^{18} are benzyl, hydrogenation of the product will yield the diacid of formula (I) wherein R and R^4 are both H. Alternatively if one of R^{17} and R^{18} is benzyl and the other is alkyl, hydrogenation will yield a monoester product. This can then be hydrolysed, if desired, to again yield the diacid product. When R^{17} or R^{18} is t-butyl, treatment of the compound of formula (V) with trifluoroacetic acid or hydrogen

chloride yields the corresponding acid. If some other carboxylic acid protecting group is used for R^{17} or R^{18} then clearly appropriate conditions for its removal must be employed in the final step to give the ester or diacid product of formula (I). For example when R^{17} or R^{18} is trimethylsilylethyl it may be removed by treatment with tetrabutylammonium fluoride. Any protecting groups present in $R^{2'}$ and $R^{3'}$ must also be removed and this may be performed concominantly with removal of protecting groups present in R^{17} and R^{18} or as a separate step using procedures appropriate to the particular protecting group employed. Thus, for example when $R^{2'}$ contains a substituted or protected amino group (for example a benzylamino, dibenzylamino, benzyloxycarbonylamino or t-butyloxycarbonylamino group) the compounds may be converted to the free amines by hydrogenation or hydrolysis as appropriate.

(b) In an alternative process, compounds of the formula (I) wherein R^2 is $R^{10}CONR^6$- are prepared by a process which involves reacting an amine of the formula:

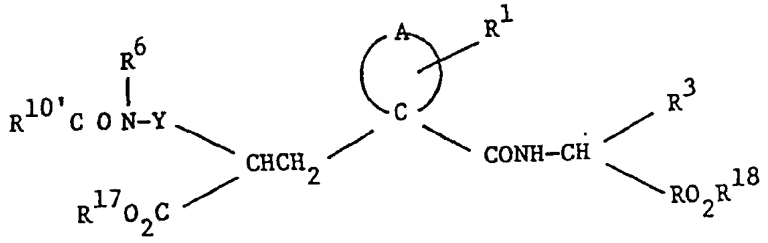


(VI)

wherein A, Y, R^1, R^3, R^6, R^{17} and R^{18} are as previously defined; with a carboxylic acid or acid chloride of the formulae:

$$R^{10}CO_2H \quad \text{or} \quad R^{10}COCl$$

wherein R^{10} is as previously defined, and wherein any reactive groups therein are optionally protected, to yield for example a compound of the formula:



(VII)

wherein $R^{10'}$ is as previously defined for R^{10} with any reactive groups therein optionally protected; and subsequently removing any protecting groups, if present and hydrolysing the ester product to yield the compounds of formula (I) wherein R and R^4 are H.

The reaction of the amine of formula (VI) and acid of formula $R^{10}CO_2H$ is achieved using conventional amide coupling techniques as previously described. In the case where R^{10} is $(R^5)_2N$, the acid chloride may be prepared by first reacting the amine with phosgene; subsequent reaction with the amine of formula (VI) yields the urea products. Subsequent removal of protecting groups is achieved using appropriate procedures as previously described.

The amines of formula (VI) are prepared following the same procedure outlined in process (a) above but using an acid of formula (III) wherein $R^{2'}$ is a protected amine. Thus, in one variant of this process, the coupling reaction with the amino acid derivative is achieved using a compound of formula (III) wherein R^2 is dibenzylamino or di(alpha-methylbenzyl)amino . Hydrogenation of the coupled product of formula (V) gives the amine of formula (VI) wherein R^6 is H.

c) Certain compounds of formula (I) are best prepared by routes which involve coupling a precursor stage to give a diester derivative of formula (V) type, which is then subjected to a chemical transformation reaction to give the particular R^2 group desired.

Thus for example the coupling process may be performed using an acid of formula (III) wherein $R^{2'}$ is halo (e.g. bromo). This may then be reacted with an amine of formula $(R^5)_2NH$ to yield the compounds wherein $R^{2'}$ is $(R^5)_2N-$, or with an azide to give compounds wherein $R^{2'}$ is N_3. Subsequent reduction of the azide group by catalytic hydrogenation, either on the protected product or on the deprotected diacid, gives the corresponding amine of formula (I) wherein R^2 is NH_2.

In another variation, an acid of formula (III) is used wherein $R^{2'}Y$- is 2-propenyl. Reaction of the coupled product of formula (V) with a (C_1-C_6)alkanol or (C_1-C_4)alkoxy(C_1-C_6)alkanol in the presence of mercuric acetate and potassium iodide yields the 3-iodo-2-[(C_1-C_6)alkoxy]- or 2-[(C_1-C_4)alkoxy(C_1-C_6)alkoxy]-propyl derivative, subsequent reduction (e.g. with tributyltin hydride) yields the corresponding compound of formula (V) wherein Y is propyl and $R^{2'}$ is (C_1-C_6)alkoxy or (C_1-C_4)alkoxy(C_1-C_6)alkoxy attached at the 2-position. In a further variant of this process the iodo intermediate can be reacted with a heterocyclic compound (e.g. imidazole) to yield the compound of formula (V) wherein R^2 is of formula R^7R^8CH, R^7 is heterocyclyl(C_1-C_4)alkyl and R^8 is (C_1-C_6)alkoxy.

Compounds of the formula (I) wherein Z is present and is S(O) or $S(O)_2$ can naturally be prepared by oxidation of the corresponding thio derivatives where Z is S. The oxidation may be performed either on the protected diester formula (V) or on the deprotected diacid product. Appropriate reagents will be well known to those skilled in the art but, for example, metachloro-peroxybenzoic acid in excess can be used to give the corresponding sulphones (Z = SO_2) or an equimolar amount of sodium metaperiodate to give the sulphoxides (Z = SO).

Appropriate reagents and conditions for all of the above transformations will be well known to those skilled in the art by reference to standard text books and to the examples provided hereafter. Other variations and possibilites for the convenient synthesis of the range of R^2 substituents will also be evident to those skilled in the art and the above are representative of some of the variations which are possible.

Compounds of the formula (I) wherein one or both of R and R^4 is a biolabile ester-forming group are prepared following similar procedures to those outlined above using the appropriate ester group for R or R^4.

As well as removing any protecting group which may be present in $R^{2'}$, a number of chemical transformation reactions are possible on the final mono-ester or diacid products as previously described. In each case the product may be obtained as the free carboxylic acid or it may be neutralised with an appropriate base and isolated in salt form.

Appropriate coupling and protecting methods for all of the above steps and alternative variations and procedures will be well known to those skilled in the art by reference to appropriate text books and to the examples provided hereafter.

The starting spiro-substituted glutaric acid mono esters of formula (III) may be prepared as described in our European patent application 274234. The amino acid esters of formula (IV) are generally known compounds which are either commercially available or they may be prepared by standard methods in accordance with literature precedents.

As previously mentioned, the compounds of the invention are potent inhibitors of the neutral endopeptidase (E.C.3.4.24.11). This enzyme is involved in the breakdown of a number of peptide hormones including, in particular the breakdown of atrial natriuretic factor (ANF). Thus, the compounds of the invention, by preventing the degradation of ANF by endopeptidase E.C.3.4.24.11, can potentiate its biological effects and the compounds are thus diuretic, natriuretic and antihypertensive

agents of utility in a number of disorders including hypertension, heart failure, angina, renal insufficiency, premenstrual syndrome, cyclical oedema, Menieres disease, hyperaldosteroneism (primary and secondary) and hypercalciuria. In addition, because of their ability to potentiate the effects of ANF the compounds have utility in the treatment of glaucoma. As a further result of their ability to inhibit the neutral endopeptidase E.C.3.4.24.11 the compounds of the invention may have activity in other therapeutic areas including for example the treatment of asthma, inflammation, pain, epilepsy, affective disorders, dementia and geriatric confusion, obesity and gastrointestinal disorders (especially diarrhoea and irritable bowel syndrome), the modulation of gastric acid secretion and the treatment of hyperreninaemia.

Activity against neutral endopeptidase E.C.3.4.24.11 is assessed using a procedure based on the assay described by J. T. Gafford, R. A. Skidgel, E. G. Erdos and L. B. Hersh, Biochemistry, 1983, 32, 3265-3271. The method involves determining the concentration of compound required to reduce by 50% the rate of release of radiolabelled hippuric acid from hippuryl-L-phenylalanyl-L-arginine by a neutral endopeptidase preparation from rat kidney.

As previously mentioned, the compounds of the invention are also inhibitors of angiotensin converting enzyme. As such they are useful in treating a further variety of conditions for which ACE inhibitors are known to be useful including limitation of ischaemic damage to the myocardium, protection of the kidney against hyperfiltration damage, prevention or reversal of left

ventricular hypertrophy, memory enhancement, control of cognitive function, dementia, and preventing reocclusion following coronory angioplasty or coronory artery bypass surgery. Their activity against this enzyme is assessed using a modified procedure based on the assay described by Rohrbach, M.S., Anal. Biochem., 1978, 84, 272. The method involves determining the concentration of compound required to reduce by 50% the extent of release of radiolabelled hippuric acid from hippuryl-L-histidyl-L-leucine by angiotensin converting enzyme isolated from the rat kidney.

Inhibitory activity is also measured in vivo following intravenous injection to anaesthetised rats using the methods described by I. L. Natoff et al, Journal of Pharmacological Methods, 1981, 5, 305 and by D. M. Gross et al, J. Pharmacol. Exp. Ther., 1981, 216, 552. The dose of inhibitor required to reduce the pressor response produced by intravenous injection of angiotensin I (50 ng bolus) by 50% is determined.

The activity of the compounds as diuretic agents is determined by measuring their ability to increase urine output and sodium ion excretion in saline loaded conscious mice. In this test, male mice (Charles River CD1, 22-28 g) are acclimatised and starved overnight in metabowls. The mice are dosed intravenously via the tail vein, with the test compound dissolved in a volume of saline solution equivalent to 2.5% of body weight. Urine samples are collected each hour for two hours in pre-weighed tubes and analysed for electrolyte concentration. Urine volume and sodium ion concentration from the test animals are compared to a control group which received only saline.

The antihypertensive activity of the compounds is evaluated

by measuring the fall in blood pressure following oral or intravenous administration to salt depleted, diuretic primed, spontaneously hypertensive rats, salt depleted renally hypertensive dogs, or DOCA/salt hypertensive rats.

For administration to man in the curative or prophylactic treatment of hypertension, congestive heart failure or renal insufficiency, oral dosages of the compounds will generally be in the range of from 3-1500 mg daily for an average adult patient (70 kg). Thus for a typical adult patient, individual tablets or capsules contain from 1 to 500 mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier for administration singly, or in multiple doses, once or several times a day. Dosages for intravenous administration would typically be within the range 1 to 500 mg per single dose as required. In practice the physician will determine the actual dosage which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case but there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

For human use, the compounds of the formula (I) can be administered alone, but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they may be administered orally in the form of tablets containing such excipients as starch or lactose, or in capsules or ovules either alone or in admixture with

excipients, or in the form of elixirs or suspensions containing flavouring or colouring agents. They may be injected parenterally, for example, intravenously, intramuscularly or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood.

The compounds may be co-administered with other agents as may be beneficial for the control of blood pressure or the treatment of cardiac conditions or renal insufficiency. Thus for example they may be co-administered with digitalis or another cardiac-stimulant drug or with an alpha-blocker, beta-blocker, exogenous ANF or with a potassium channel activator or another diuretic agent as shall be determined by the physician as appropriate to the particular patient or disease state.

Thus in a further aspect the invention provides a pharmaceutical composition comprising a compound of the formula (I) or (II), or a pharmaceutically acceptable salt thereof or bioprecursor therefor, together with a pharmaceutically acceptable diluent or carrier.

The invention also includes a compounds of the formula (I) or (II), or a pharmaceutically acceptable salt thereof or bioprecursor therefor, for use in medicine, in particular in the treatment of hypertension, congestive heart failure or renal insufficiency in a human being.

The preparation of the compounds of the invention and of intermediates for use in their preparation is illustrated by the

following Examples. Thin layer chromatography was performed on silica plates using the following solvent systems: ethyl acetate, hexane, 1:1(ss 1); ethyl acetate, hexane, 1:3(ss-2); methyl isobutyl ketone, water, acetic acid, 2:1:1,(ss 3); diethyl ether, hexane, 3:7(ss 4); ethyl acetate(ss 5); diethyl ether(ss 6); dichloromethane, methanol, acetic acid, 80:20:1(ss 7), diethyl ether, hexane, 1:1(ss 8), hexane, ethyl acetate, 4:1 (ss 9), or n-butanol, acetic acid, water, 12:3:5 (ss 10)

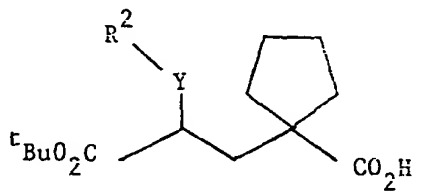
EXAMPLE 1

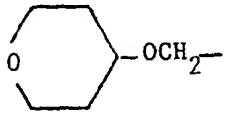
1-(2-t-Butoxycarbonyl-4-ethoxybutyl)cyclopentane carboxylic acid

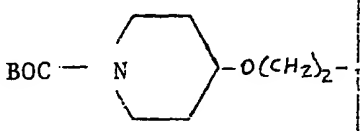
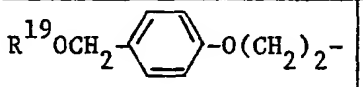
A solution of t-butyl 3-(1-carboxycyclopentyl)propanoate (3.0 g, 12.38 mmol) in dry tetrahydrofuran (10 ml) was added to a stirred solution of lithium diisopropylamide (26 mmol) in a mixture of hexane (10.4 ml) and tetrahydrofuran (45 ml) at -70°C under nitrogen. After 1 hour a solution of 2-iodo-1-ethoxyethane (4.95 g, 24.8 mmol) in dry tetrahydrofuran (10 ml) was added maintaining the temperature at -70°C. After an hour at that temperature, the solution was allowed to warm up to room temperature overnight and left for a further two days. The mixture was then acidified to pH 2 with 2N hydrochloric acid, and extracted with ether. The organic extract was washed with brine, dried ($MgSO_4$) and the solvent evaporated to give the crude acid which was chromatographed on silica. Elution with increasing proportions of ethyl acetate in hexane (1:4 to neat ethyl acetate) gave an oil (2.5 g, 55%). Rf 0.15 hexane, ethyl acetate, 4:1). Found: C,65.10; H,9.36. $C_{17}H_{30}O_5$ requires C,64.94; H,9.62%.

EXAMPLES 2-8

The following compounds were prepared by alkylating 1-carboxy-cyclopentylpropanoic acid t-butyl ester using the appropriate bromo or iodocompound following the procedure of Example 1.



Example No	R^2-Y-	Form isolated T.L.C.	Analysis % (Theoretical in brackets) C	H	N
2		oil Rf 0.3 (ss 1)	64.43 (64.02	8.82 9.05)	
3	$CH_3O(CH_2)_4O(CH_2)_2$-	oil Rf 0.45 (ss 1)	64.24 (64.49	9.90 9.74)	
4	$CH_3OCH_2CH=CHCH_2O(CH_2)_2$-	oil Rf 0.45 (ss 1)	62.36 (62.62 (0.2 mole CH_2Cl_2)	8.83 8.95)	
5	$Br(CH_2)_6$-	oil Rf 0.5 (ss 2)	-		

6		oil Rf 0.4 (ss 1)	61.86 8.89 3.36 (61.79 8.93 2.80) (0.25 mole CH_2Cl_2)
7	$Br(CH_2)_8-$	oil Rf 0.9 (ss 3)	58.08 8.60 (58.15 8.60)
8		oil Rf 0.9 (ss 1)	65.36 8.97 (65.20 9.19) (0.5 mole H_2O)

BOC = t-butoxycarbonyl

R^{19} = dimethyl-t-butylsilyl

EXAMPLE 9

1-[2(RS)-t-Butoxycarbonyl-10-azidodecyl]-1-cyclopentane carboxylic acid

Tetramethylguanidinium azide (0.7 g, 6 mmol) was added as a solution in chloroform (10 ml) to a solution of 1-[2(RS)-t-butoxycarbonyl-10-bromodecyl]-1-cyclopentane carboxylic acid (1.4 g, 3 mmol) in chloroform (10 ml). A few crystals of potassium iodide were added and the resulting mixture was refluxed for 2½ days. The cooled reaction mixture was then diluted with

chloroform (20 ml) and washed with water (2 x 20 ml), dried ($MgSO_4$), filtered and evaporated. The residue was chromatographed on silica gel using a gradient of ethyl acetate and hexane to give the title compound as an oil (0.69 g, 54%). Found: C,63.84; H,9.41; N,9.22. $C_{21}H_{37}N_3O_4$ requires C,63.77; H,9.43; N,10.62%. Rf 0.9 (ethyl acetate).

EXAMPLE 10

1-((2R)-t-Butoxycarbonyl-4-pentenyl)cyclopentanecarboxylic acid

A mixture of 1-(2(R,S)-t-butoxycarbonyl-4-pentenyl)cyclopentane carboxylic acid (EP-A-0274234, Example 44) (28.24 g, 0.1 mmol) and (+)- pseudoephedrin were recrystallised three times from hexane to give a white crystaline solid (18.9 g, 42%) m.p. 106.5-107.5°C. $[\alpha]_D^{25}$ + 20.5° $[\alpha]_{365}^{25}$ + 70.7° (c = 1.07, methanol).

The above salt was dissolved in ether and washed with 1N hydrochloric acid and saturated salt solution. Drying ($MgSO_4$) and evaporation gave the required R-acid as an oil (11.9 g). Rf 0.7 (ethyl acetate, hexane, 1:1). $[\alpha]_D^{25}$ - 11.8°, $[\alpha]_{365}^{25}$ - 36.5° (c = 1.03, methanol).

EXAMPLE 11

1-[2(RS)-t-Butoxycarbonyl-4-pentenyl]-1-cyclopentane carboxylic acid benzyl ester

Anhydrous potassium carbonate (13.5 g, 98 mmol) was added in one portion to a stirred and ice-cooled solution of 1-[2(RS)-t butoxycarbonyl-4-pentenyl]-1-cyclopentane carboxylic acid (10.95 g, 38 mmol) and benzyl bromide (6.6 g, 38 mmol) in dry dimethylformamide (30 ml). After 3 hours the reaction mixture was diluted

with ethyl acetate (100 ml) and water (100 ml). The organic phase was separated and washed with further portions of water (1 x 20 ml) 1M hydrochloric acid (5 x 20 ml), brine (1 x 10 ml), dried ($MgSO_4$), and the solution filtered and evaporated to yield the title compound as an oil (14.14 g, 98%). This oil was used without further purification. Rf 0.86 (ethylacetate, toluene, 1:4).

EXAMPLE 12

1-[2(RS)-t-Butoxycarbonyl-4-oxobutyl]-1-cyclopentane carboxylic acid benzyl ester

Osmium tetroxide (56 mg, 0.2 mmol) was added as a 2.5% w/v solution in t-butanol (2.25 ml) to a stirred solution of 1-[2(RS)-t-butoxycarbonyl-4-pentenyl]1-cyclopentane carboxylic acid benzyl ester (8.25 g, 22 mmol) in acetonitrile (60 ml) and water (10 ml) at room temperature. After 30 minutes, the black-brown solution was treated with sodium metaperiodate (10 g, 47 mmol) in one portion. Stirring was continued for 18 hours and then the suspended solid was filtered and washed with a small portion of acetonitrile. The filtrate was evaporated and the dark residue was chromatographed on silica gel eluting with a gradient of ethyl acetate and hexane to yield the title compound as an oil (3.77 g, 45%). Rf 0.58 (diethyl ether, petrol, 1:1).

EXAMPLE 13

1-[2(RS)-t-Butoxycarbonyl-3-carboxypropyl]-1-cyclopentane carboxylic acid benzyl ester

Potassium permanganate (7.6 g, 48 mmol) as a solution in water (48 ml) was added slowly to a stirred solution of 1-[2(RS)-t-butoxycarbonyl-4-oxobutyl]-1-cyclopentane carboxylic acid benzyl ester (51 g, 12 mmol) in t-butanol (70 ml) and 1M sodium dihydrogen phosphate buffer solution (20 ml). The resulting mixture was stirred vigorously for 30 minutes. Excess oxidant was destroyed by the addition of solid sodium metabisulphate (8 g). The brown suspension was filtered, the filter pad being washed with ethyl acetate (50 ml). The filtrate was separated into two phases and the aqueous phase was extracted with ethylacetate (30 ml). The combined organic solutions were dried ($MgSO_4$), filtered and evaporated to give the title compound as an oil (4.52 g, 96%). Rf 0.7 (ss 5).

EXAMPLE 14

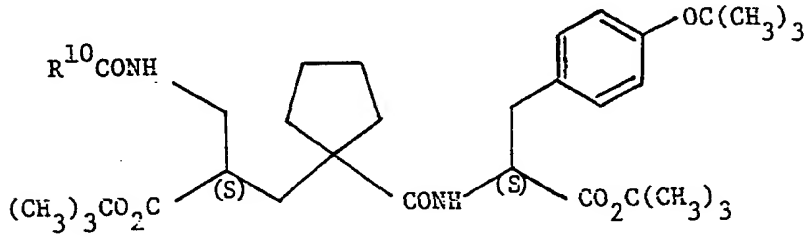
N-{1-{3-[4-(t-Butoxycarbonylaminomethyl)benzoylamino]-2(S)-t-butoxycarbonylpropyl}-1-cyclopentanecarbonyl}-O-t-butyl-(S)-tyrosine-t-butyl ester

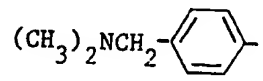
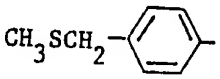
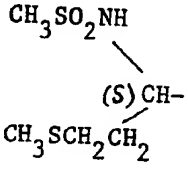
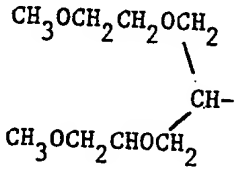
To an ice-cold solution of 4-t-butoxycarbonylaminomethyl-benzoic acid (0.689 g, 2.74 mmol) in dry dichloromethane (30 ml) was added 1-hydroxybenztriazole (0.409 g, 3.02 mmol), 1-ethyl-3-(dimethylaminopropyl)-carbodiimide (0.684 g, 3.57 mmol) and N-methylmorpholine (0.360 g, 3.57 mmol) and the resulting solution stirred at 0°C for 30 minutes. N-[1-(3-Aminopropyl-2(S)-t-butoxycarbonyl)-1-cyclopentanecarbonyl]-O-t-butyl-(S)-tyrosine

t-butyl ester was added to this solution and stirred at room temperature for 24 hours. The solvent was evaporated under reduced pressure and the resultant oil dissolved in ethyl acetate (80 ml) and washed with 2M hydrochloric acid (50 ml), saturated aqueous sodium bicarbonate (2 x 50 ml) and saturated brine (50 ml), dried ($MgSO_4$) and the solution filtered and evaporated to yield the crude product as an oil. Chromatography on silica gel using dichloromethane/diethyl ether as eluent gave the title compound (1.695 g, 79%) as a white foam. Rf 0.52 (dichloromethane, diethyl ether, 1:1). Found: C,67.52; H,8.47; N,5.26. $C_{44}H_{65}N_3O_9$ requires C,67.75; H,8.40; N,5.39%.

EXAMPLES 15-18

The following compounds were prepared following the procedure of Example 14, using the appropriate carboxylic acid derivative of formula $R^{10}CO_2H$.



Example No	R^{10}	Form isolated T.L.C.	Analysis % (Theoretical in brackets) C	H	N
15		foam Rf 0.38 (ss 3)	69.21 (69.55	8.70 8.68	5.65 5.93)
16		foam Rf 0.85 (ss 5)	67.57 (67.25	8.22 8.08	3.94 4.02)
17		foam Rf 0.83 (ss 5)	58.52 (58.78	8.00 8.13	5.39 5.56)
18		foam 0.29 (ss 5)	64.70 (64.37	8.89 8.96	3.69 3.66)

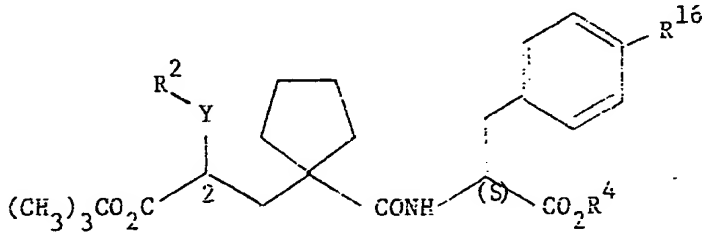
EXAMPLE 19

N-[1-{4-Ethoxy-2-(t-butoxycarbonyl)butyl}-cyclopentanecarbonyl]--O-methyl-(S)-tyrosine t-butyl ester

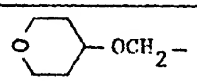
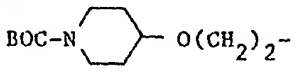
1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (762 mg, 3.98 mmol) was added to an ice cold stirred mixture of 1-(2-t-butoxycarbonyl-4-ethoxybutyl)cyclopentane carboxylic acid from Example 1 (626 mg, 1.99 mmol), O-methyl-(S)-tyrosine t-butyl ester (500 mg, 1.99 mmol), 1-hydroxybenzotriazole (269 mg, 1.99 mmol) and N-methylmorpholine (0.44 ml, 3.98 mmol) in dry methylenechloride (10 ml). After standing at room temperature for 16 hours the mixture was diluted with methylene chloride, washed with water, dried ($MgSO_4$) and evaporated under reduced pressure to give an oil. Chromatography on silica gel, eluting with a mixture of hexane and ethyl acetate (4:1) gave the pure diester (975 mg; 89%) as an oil. Found: C,67.54; H,8.74; N,2.13. $C_{31}H_{49}NO_7$. 0.25 H_2O requires C,67.42; H,9.03; N,2.53%.

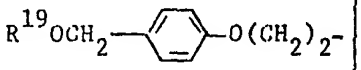
EXAMPLES 20-29

The following compounds were prepared as described above using the appropriate cyclopentane carboxylic acid of Examples 1-6 and 8-10 in the coupling step together with the appropriate amine of formula (IV).



Examples 25 and 26 are the 2(R) isomers, Example 28 is the 2(S) isomer.

Example No	R^2-Y-	R^{16}	R^4	Form Isolated T.L.C.	Analysis (Theoretical in brackets) C	H	N
20		$(CH_3)_3CO$-	$(CH_3)_3C$-	oil Rf = 0.6 (ss 1)	68.11 (68.43	8.70 9.09	2.17 2.22)
21	$CH_3O(CH_2)_4O(CH_2)_2$-	$(CH_3)_3CO$-	$(CH_3)_3C$-	oil Rf = 0.7 (ss 1)	67.14 (67.40	9.08 9.15	2.48 2.31)
22	$CH_3OCH_2CH=CHCH_2O(CH_2)_2$-	CH_3O-	$(CH_3)_3C$-	oil Rf = 0.7 (ss 1)	67.34 (67.63	8.63 8.85	2.46 2.32)
23	$Br(CH_2)_6$-	CH_3O-	$(CH_3)_3C$-	oil Rf = 0.4 (ss 4)	62.57 (62.00	8.49 8.20	2.31 2.19)
24		CH_3O-	$(CH_3)_3C$-	oil Rf = 0.75 (ss 1)	64.55 (64.63 (0.2 mole CH_2CH_2,	8.42 8.70 0.5 mole H_2O)	4.10 3.85)
25	$CH_2=CH-CH_2$-	CH_3O-	$(CH_3)_3C$-	oil Rf = 0.2 (ss 2)	69.41 (69.38 (0.2 mole H_2O)	8.76 8.81	2.74 2.70)

26	$CH_2=CH-CH_2$	$(CH_3)_3CO-$	$(CH_3)_3C-$	oil Rf = 0.3 (ss 4)	71.26 (71.06	9.16 9.22	2.34 2.51)
27	$N_3(CH_2)_8-$	$(CH_3)_3CO-$	CH_3CH_2-	oil Rf = 0.85 (ss 5)	-		
28	$CH_3O(CH_2)_2OCH_2-$	CH_3O-	CH_3CH_2-	oil Rf = 0.6 (ss 6)	64.65 (65.02	8.42 8.47	2.32 2.61)
29		CH_3O-	$(CH_3)_3C-$	oil Rf = 0.4 (ss 9)	-		

EXAMPLE 30

N-[1-{2(S)-t-Butoxycarbonyl)-5-iodo-4-(2-methoxyethoxypentyl}-1-cyclopentanecarbonyl]-O-t-butyl-(S)-tyrosine t-butyl ester

Mercuric acetate (662 mg, 2.08 mmol) was added to a stirred solution of the diester from Example 26 (892 mg, 1.6 mmol) in 2-methoxyethanol (4 ml). After 20 hours at room temperature, 2N sodium hydroxide (3.6 ml) was added followed by potassium iodide (2.9 g, 17.5 mmol) dissolved in water (3 ml). The mixture was diluted with water, extracted with diethyl ether and the extract washed with water. Drying over $MgSO_4$ and evaporation gave an oil which was dissolved in carbon tetrachloride. Iodine (406 mg, 1.6 mmol) was added and the solution stirred for six hours. The mixture was then filtered, evaporated under reduced pressure and the residue chromatographed on silica. Elution with a mixture of diethyl ether and hexane (4:6) gave the title product as an oil (620 mg, 51%). Rf 0.35 (diethyl ether, hexane, 1:1).

EXAMPLE 31

N-[1-{2(S)-t-Butoxycarbonyl)-5-iodo-4-(2-methoxyethoxypentyl}-1-cyclopetanecarbonyl]-O-methyl-(S)-tyrosine t-butyl ester

The title compound was prepared from Example 25 using the procedure of Example 30 above. The product was obtained as an oil (57% yield). Rf 0.28, (diethyl ether, hexane, 1:1). Found: C,55.60; H,6.99; N,1.92. $C_{33}H_{52}INO_8$ requires C,55.23; H,7.30; N,1.95%.

EXAMPLE 32

N-[1-{2(S)-(t-Butoxycarbonyl)-4-(2-methoxyethoxy)pentyl}-1-cyclopentanecarbonyl]-O-t-butyl-(S)-tyrosine t-butyl ester

Tributyltin hydride (0.5 ml, 1.86 mmol) was added to a solution of the iodo compound from Example 30 (590 mg, 0.78 mmol) in dry tetrahydrofuran (10 ml). After heating at 55°C for 16 hours, the solution was diluted with diethyl ether, washed with dilute potassium fluoride solution (x4) and then with saturated salt solution. Drying ($MgSO_4$) and evaporation under reduced pressure gave an oil which was chromatographed on silica. Elution with a mixture of diethyl ether and hexane (1:1) gave the required product as an oil (410 mg, 83%). Rf 0.32 (ether/hexane 1:1). Found: C,68.00; H,9.25; N,2.25. $C_{36}H_{59}NO_8$ requires C,68.21; H,9.38; N,2.21%.

EXAMPLE 33

N-[1-{2(S)-(tert-Butoxycarbonyl)-4(2-methoxyethoxy)pentyl}-1-cyclopentanecarbonyl]-O-methyl-(S)-tyrosine tert-butyl ester

A solution of the iodo compound from Example 31, (430 mg, 0.6 mmol) in ethyl acetate (30 ml) containing triethylamine (67 mg, 0.66 mmol) was hydrogenated over 10% palladium on charcoal at room temperature at 50 p.s.i. (3.45 bar) pressure. The mixture was filtered, the solvent evaporated and the residue chromatographed on silica to give the title compound as an oil (300 mg, 85%) Rf 0.2 (diethyl ether, hexane, 1:1).

EXAMPLE 34

N-[1-{2(S)-(t-Butoxycarbonyl)-5-(1-imidazolyl)-4-methoxypentyl}-1-cyclopentanecarbonyl]-O-methyl-(S)-tyrosine t-butyl ester

a) Mercuric acetate (797 mg, 2.5 mmol) was added to a solution of the diester of Example 25 (1.14 g, 2.21 mmol) in dry methanol (5 ml). After stirring for an hour at room temperature, 2N sodium hydroxide (5.5 ml) was added followed by potassium iodide (1.83 g, 11.05 mmol) dissolved in water (2.5 ml). Water was added and the mixture extracted with ether. The organic extract was washed with water, dried ($MgSO_4$) and evaporated to give an oil, which was dissolved in carbon tetrachloride. Iodine (558 mg, 2.2 mmol) was added and after stirring at 0°C under nitrogen for 1.5 hours, the solvent was evaporated under reduced pressure. The residue was chromatographed on silica, eluting with a mixture of diethyl ether and hexane (4:6) to give N-[1-{2(S)-(t-butoxycarbonyl)-5-iodo-4-methoxypentyl}-1-cyclopentanecarbonyl]-(S)-O-methyl-tyrosine t-butyl ester as an unstable oil (1.27 g, 85%). Rf 0.37 (diethyl ether, hexane, 1:1) which was used directly for the next step.

b) A solution of the above iodide (620 mg, 0.92 mmol) and imidazole (627 mg, 9.2 mmol) in acetonitrile (12 ml) was refluxed for 24 hours. Evaporation of the solvent under reduced pressure gave a gum which was chromatographed on silica. Elution with a mixture of ethanol and ethyl acetate (1:19) gave the title product as a gum. Rf 0.4 (ethanol, ethyl acetate, 1:9). Found: C,66.05; H,8.22; N,6.80. $C_{34}H_{51}N_3O_7$ requires C,66.53; H,8.37; N,6.85%.

EXAMPLE 35

N-[1-{8-Morpholino-2-(t-butoxycarbonyl)octyl}-1 cyclopentane carboxy]-(S)-O-methyltyrosine t-butyl ester

The bromo compound from Example 23 (1.2 g, 1.88 mmol) and morpholine (650 mg, 7.5 mmol) were heated at 50°C in dimethylformamide (15 ml) containing potassium iodide (120 mg). After 20 hours, water was added and the mixture extracted with ethyl acetate. Washing with water, drying ($MgSO_4$) and evaporation gave an oil (1.2 g) which was chromatographed on silica. Gradient elution starting with hexane, ethyl acetate (7:3) progressing to neat ethyl acetate and finally with ethyl acetate, ethanol, (95:5) gave the required compound as a gum (1.0 g). Rf 0.3 (hexane, diethyl ether, 1:1). Found: C,68.10; H,9.50; N,4.14. $C_{37}H_{60}N_2O_7 \cdot 0.5\ CH_3CO_2C_2H_5$ requires C,68.09; H,9.37; N,4.30%.

EXAMPLE 36

N-[1-2(S)-t-Butoxycarbonyl-3-(diethylaminocarbonylamino)propyl-1-cyclopentanecarbonyl]-O-methyl-(S)-tyrosine t-butyl ester

Phosgene (72 mg, 0.7 mmol) as a 12.5% w/v solution in toluene (0.6 ml) was added in one portion to a stirred and cooled solution of diethylamine (85 mg, 0.65 mmol) and N-methyl morpholine (73 mg, 0.7 mmol) in methylene chloride (10 ml). After stirring at 0°C for 2 hours, nitrogen was bubbled gently through the solution to remove excess phosgene. To this solution at room temperature was added more N-methylmorpholine (73 mg, 0.7 mmol) and N-[1-(3-aminopropyl-2(S)-t-butoxycarbonyl)-1-cyclopentane-carbonyl]-O-t-butyl-(S)-tyrosine t-butyl ester (360 mg, 0.65 mmol)

as a solution in methylene chloride (3 ml). After stirring at room temperature overnight, the solvent was evaporated and the residue was dissolved in ethyl acetate (15 ml). This solution was washed with water (2 x 5 ml), 1M hydrochloric acid (2 x 5 ml), saturated sodium bicarbonate solution (1 x 5 ml), brine (1 x 5 ml), dried ($MgSO_4$), filtered and evaporated. The residual oil was chromatographed on silica gel using a gradient of methylene chloride and methanol saturated with aqueous ammonia to give the title compound as an oil (332 mg, 82%). Rf 0.67 (ethyl acetate).

EXAMPLE 37

N-[1-(2(RS)-t-Butoxycarbonyl-3-{4-keto-1-piperidylcarbonyl}propyl)-1-cyclopentanecarbonyl]-O-methyl-(S)-tyrosine t-butyl ester

a) 4-Piperidone was coupled to 1-[2(RS)-t-butoxycarbonyl-3-carboxypropyl]-1-cyclopentanecarboxylic acid benzyl ester (Example 13) using the procedure of Example 14 to give 1-[2(RS)-t-butoxycarbonyl-3-(4-keto-1-piperidylcarbonyl)propyl]1-cyclopentane carboxylic acid benzyl ester.

b) The above product was dissolved in an ethanol, water mixture (9:1) and hydrogenated at room temperature under an atmosphere of hydrogen (60 p.s.i., 4.1 bar) over 10% palladium on carbon for 3 hours. The reaction mixture was filtered, and the filtrate evaporated to dryness. The residue was azeotroped with dichloromethane to yield 1-(2(RS)-t-butoxycarbonyl-3-(4-keto-1-piperidylcarbonyl)propyl)-1-cyclopentane-carboxylic acid as a foam. Rf 0.21 (ethyl acetate). Found: C,62.42; H,8.02; N,3.67. $C_{34}H_{50}N_2O_8$ requires C,62.97; H,8.19; N,3.67%.

c) The above acid was coupled to O-methyl-(S)tyrosine-t-butyl ester following the procedure of Example 19 to yield the title product as a foam, Rf 0.71 (ethyl acetate).

EXAMPLE 38

N-[1-(2(RS)-t-Butoxycarbonyl-3-(4-hydroxy-1-piperidinylcarbonyl)-propyl)-1-cyclopentanecarbonyl]-O-methyl-(S)tyrosine t-butyl ester

1M Hydrochloric acid was added to a stirred ice-cooled solution of N-[1-(2(RS)-t-butoxycarbonyl-3-(4-keto-1-piperidyl-carbonyl)propyl)-1-cyclopentanecarbonyl]-O-methyl-(S)-tyrosine t-butyl ester (400 mg, 0.6 mmol) in ethanol (3 ml) and water (2 ml) to adjust the pH of the solution to between 4 and 6. More ethanol was added as necessary to maintain a homogeneous solution. To the above solution was added sodium cyanoborohydride (45 mg, 0.7 mmol) in one portion. The resulting mixture was allowed to warm to room temperature overnight. The ethanol was evaporated and the aqueous residue was partitioned between ethyl acetate (20 ml) and water 20 (ml). The organic phase was separated and washed with water (1 x 10 ml), 1M hydrochloric acid (2 x 10 ml), saturated sodium bicarbonate solution (1 x 10 ml), brine (1 x 10 ml), dried ($MgSO_4$) and filtered. The filtrate was evaporated and the residue was chromatographed on silica gel eluting with a gradient of ethyl acetate and hexane to yield the title compound as a gum (160 mg, 38%). Rf 0.29 (ethyl acetate).

EXAMPLE 39

N-[1-(2(RS)-t-Butoxycarbonyl-3-(4-dimethylamino-1-piperidyl-carbonyl)propyl)-1-cyclopentanecarbonyl]-O-methyl-(S)tyrosine t-butyl ester

Sodium cyanoborohydride (60 mg, 0.9 mmol) was added in one portion to a stirred and ice-cooled mixture of N-[1-(2(RS)-t-butoxycarbonyl-3-(4-keto-1-piperidylcarbonyl)propyl)-1-cyclopentanecarbonyl]-O-methyl-(S)tyrosine t-butyl ester (550 mg, 0.9 mmol) from Example 37), anhydrous sodium acetate (730 mg, 9 mmol, and dimethylamine hydrochloride (360 mg, 4.5 mmol) in dry methanol (15 ml). The mixture was allowed to warm to room temperature. After 24 hours, the solvent was evaporated and the residue partitioned between ethyl acetate (50 ml) and water (30 ml). The organic layer was separated and washed with water (1 x 10 ml), saturated sodium bicarbonate solution (2 x 15 ml), brine (1 x 10 ml), dried ($MgSO_4$) and filtered. The filtrate was evaporated and the crude residue was chromatographed on silica gel to yield the title product as a gum (313 mg, 54%). Rf 0.32 (SS 3).

EXAMPLE 40

N-[1-{2(S)-t-Butoxycarbonyl-3-(4-methanesulphonylmethylbenzoyl-amino)propyl}-1-cyclopentanecarbonyl]-O-t-butyl-(S)-tyrosine t-butyl ester

90% Metachloroperoxybenzoic acid (0.29 g, 1.5 mmol) was added in one portion to a stirred and ice-cooled solution of N-[1-2(S)-t-butoxycarbonyl-3-(4-methylthiomethylbenzoylamino)propyl -1-cyclopentanecarbonyl]-O-t-butyl-(S)-tyrosine t-butyl ester. (Example 16, 0.38 g, 0.5 mmol) in methylene chloride (10 ml). The solution was allowed to warm to room temperature overnight. The

solvent was evaporated and the residue was dissolved in ethyl acetate (20 ml). This solution was washed with saturated sodium bicarbonate solution (2 x 10 ml), 10% aqueous sodium carbonate solution (1 x 10 ml), brine (1 x 10 ml), dried ($MgSO_4$), filtered and evaporated to give the title compound as a white foam (0.39 g, 100%). Found: C,63.21; H,7.46; N,3.58. $C_{40}H_{58}N_2O_9S.\ H_2O$ requires C,63.13; H,7.94; N,3.68%. Rf 0.66 (ethyl acetate).

EXAMPLE 41

N-[1-(2(S)-t-Butoxycarbonyl-3-(2(S)-methanesulphonamido-4-methanesulphonylbutyrylamino)propyl)-1-cyclopentanecarbonyl]-O-t-butyl-(S)-tyrosine t-butyl ester

The title compound was prepared from Example 17 by oxidation with metachloroperoxybenzoic acid following the procedure of Example 40 and was obtained as a foam. Rf 0.63 (ethyl acetate). Found: C,56.09; H,7.47; N,5.58. C H N S requires C,56.39; H,7.80; N,5.33%.

EXAMPLE 42

N-[1-{2-(t-Butoxycarbonyl)-4-(4-hydroxymethylphenoxy)butyl}-1-cyclopentanecarbonyl]-O-methyl-(S)-tyrosine t-butyl ester

1M Tetrabutylammonium fluoride (2.16 ml) was added at 10°C under nitrogen to a stirred solution of the product of Example 29 (800 mg, 1.08 mmol) in tetrahydrofuran (10 ml). After standing at room temperature for 2½ days, the mixture was diluted with ethyl acetate, washed with 0.5N hydrochloric acid followed by water, dried ($MgSO_4$) and the solvent evaporated under reduced pressure. The residue was chromatographed on silica, eluting with increasing

following Examples. Thin layer chromatography was performed on silica plates using the following solvent systems: ethyl acetate, hexane, 1:1(ss 1); ethyl acetate, hexane, 1:3(ss-2); methyl isobutyl ketone, water, acetic acid, 2:1:1,(ss 3); diethyl ether, hexane, 3:7(ss 4); ethyl acetate(ss 5); diethyl ether(ss 6); dichloromethane, methanol, acetic acid, 80:20:1(ss 7), diethyl ether, hexane, 1:1(ss 8), hexane, ethyl acetate, 4:1 (ss 9), or n-butanol, acetic acid, water, 12:3:5 (ss 10)

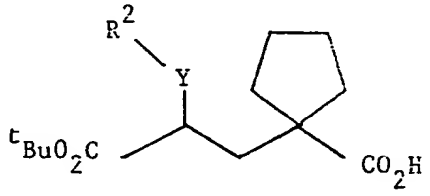
EXAMPLE 1

1-(2-t-Butoxycarbonyl-4-ethoxybutyl)cyclopentane carboxylic acid

A solution of t-butyl 3-(1-carboxycyclopentyl)propanoate (3.0 g, 12.38 mmol) in dry tetrahydrofuran (10 ml) was added to a stirred solution of lithium diisopropylamide (26 mmol) in a mixture of hexane (10.4 ml) and tetrahydrofuran (45 ml) at -70°C under nitrogen. After 1 hour a solution of 2-iodo-1-ethoxyethane (4.95 g, 24.8 mmol) in dry tetrahydrofuran (10 ml) was added maintaining the temperature at -70°C. After an hour at that temperature, the solution was allowed to warm up to room temperature overnight and left for a further two days. The mixture was then acidified to pH 2 with 2N hydrochloric acid, and extracted with ether. The organic extract was washed with brine, dried ($MgSO_4$) and the solvent evaporated to give the crude acid which was chromatographed on silica. Elution with increasing proportions of ethyl acetate in hexane (1:4 to neat ethyl acetate) gave an oil (2.5 g, 55%). Rf 0.15 hexane, ethyl acetate, 4:1). Found: C,65.10; H,9.36. $C_{17}H_{30}O_5$ requires C,64.94; H,9.62%.

EXAMPLES 2-8

The following compounds were prepared by alkylating 1-carboxy-cyclopentylpropanoic acid t-butyl ester using the appropriate bromo or iodocompound following the procedure of Example 1.



proportions of ethyl acetate in hexane (from 3:7 to 1:1) to give a clear oil (610 mg, 90%). Rf 0.4 (hexane, ethyl acetate, 1:1). Found: C,69.47; H,8.01; N,2.31. $C_{36}H_{51}NO_3$ requires C,69.09; H,8.21; N,2.24%.

EXAMPLE 43

N-[1-{2-(t-Butoxycarbonyl)-4-(4-{bis-t-butoxycarbonylaminomethyl}-phenoxy)butyl}-1-cyclopentanecarbonyl]-O-methyl-(S)-tyrosine t-butyl ester

Di-t-butyliminodicarboxylate (333 mg, 1.53 mmol) and triphenylphosphine (402 mg, 1.53 mmol) were added at 10°C under nitrogen to a stirred solution of the product of Example 42 (640 mg, 1.023 mmol) in tetrahydrofuran (6 ml). Diethyldiazodicarboxylate (0.24 ml, 1.53 mmol) in tetrahydrofuran (2 ml) was slowly added dropwise and the mixture stirred for 20 hours at room temperature. The mixture was then evaporated to dryness, the residue preabsorbed on silica and chromatographed. Elution with increasing proportions of ethyl acetate in hexane (from 5:95 to 1:4) gave the required product as a clear gum (166 mg, 20%) Rf 0.55. (hexane, ethyl acetate, 1:1).

EXAMPLE 44

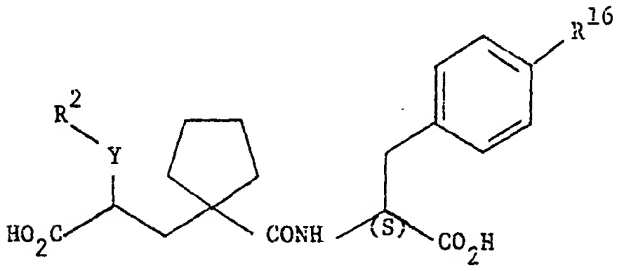
N-[1-{2(S)-Carboxy-4-(2-methoxyethoxy)pentyl}-1-cyclopentane-carbonyl]-(S)-tyrosine

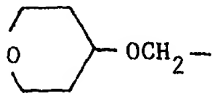
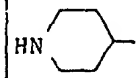
Trifluoroacetic acid (5 ml) was added to an ice cold solution of N-[1-{2(S)-t-butoxycarbonyl)-4-(2-methoxyethoxy)pentyl}-cyclopentanecarbonyl]-O-t-butyl-(S)-tyrosine t-butyl ester (from Example 32, 390 mg, 0.62 mmol) and anisole (998 mg, 9.2 mmol) in dry methylenechloride (5 ml). After standing at 0°C overnight the solution was evaporated to dryness under reduced pressure and dried azeotropically with toluene. The residual gum was dissolved in ether and the product was extracted with 1N sodium hydroxide (10 ml). The basic extract was then acidified with concentrated hydrochloric acid, saturated with salt and extracted with ethyl acetate. Washing with brine, drying ($MgSO_4$) and evaporation gave a glass which was crushed to a white powder (275 mg). Rf 0.52 (ss 7). Found: C,61.22; H,7.52; N,2.99. $C_{24}H_{35}NO_8$, 0.1 $CH_3CO_2C_2H_5$, 0.25 H_2O requires C,61.20; H,7.64; N,2.92%.

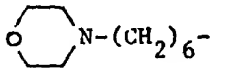
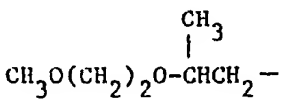
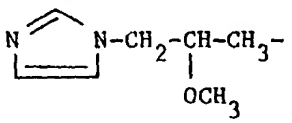
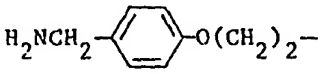
EXAMPLES 45-53

The following compounds were prepared from the corresponding O-methyl or O-t-butyl tyrosine t-butyl ester, derivative as

appropriate by treatment with trifluoroacetic acid following the procedure of Example 44. Examples 49, 50, 52 and 53 were purified by ion-exchange chromatography using Dowex AG 50W - X8 resin and eluting with 5% aqueous pyridine. Examples 51 and 52 are the 2S isomers.



Example No	R^2-Y-	R^{16}	Form Isolated T.I.C.	Analysis (Theoretical in brackets) C	H	N
45	$CH_3CH_2O(CH_2)_2$-	CH_3O-	foam 0.3 CF_3CO_2H Rf 0.2 (ss 7)	60.11 (60.03	7.07 7.09	3.14 2.96)
46		HO-	foam 0.4 CF_3CO_2H Rf 0.15 (ss 7)	58.49 (58.50	6.80 6.61	2.64 2.75)
47	$CH_3O(CH_2)_4O(CH_2)_2$-	CH_3O-	gum Rf 0.4 (ss 7)	62.52 (62.69	7.87 7.99	2.80 2.81
48	$CH_3OCH_2CH{=}CHCH_2O(CH_2)_2$-	CH_3O-	gum 0.125 CH_2Cl_2, 0.5 H_2O Rf 0.37 (ss 7)	61.55 (61.38	7.34 7.54	2.78 2.74)
49		CH_3O-	foam Rf 0.25 (ss 7)	63.35 (63.65	7.36 7.81	6.01 5.71)

50		CH_3O-	foam H_2O Rf 0.4 (ss 7)	63.38 (63.20	8.03 8.42	5.02 5.08)
51		CH_3O-	gum 0.25 H_2O Rf 0.42, 9.47 (ss 7)	62.01 (62.03	7.58 7.81	2.86 2.89)
52		CH_3O-	powder Rf 0.3 (ss 3)	61.99 (62.26	6.99 7.03	8.15 8.38)
53		CH_3O-	foam Rf 0.03 (ss 7)	64.43 (64.47	6.87 7.15	4.88 5.37)

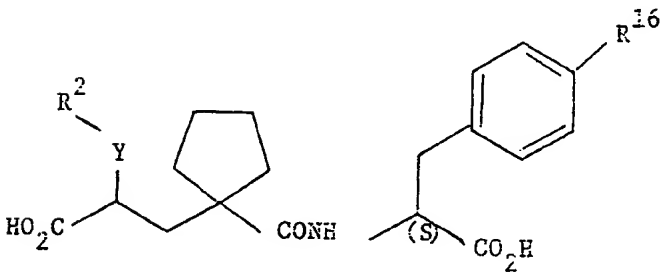
EXAMPLE 54

N-[1-(2(S)-Carboxy-3-{2(S)-methanesulphonamido-4-methane-sulphonyl-butyrylamino}propyl)-1-cyclopentanecarbonyl]-(S)-tyrosine

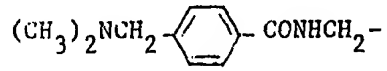
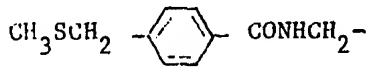
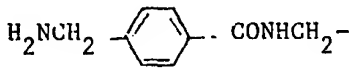
Hydrogen chloride gas was passed gently through a stirred and ice-cooled solution of N-[1-(2(S)-t-butoxycarbonyl-3-{2(S)-methanesulphonamido-4-methanesulphonylbutyrylamino}propyl)-1-cyclopentane-carbonyl]-O-t-butyl-(S)-tyrosine t-butyl ester (227 mg, 0.29 mmol) and anisole (470 mg, 4.3 mmol) in dry dichloromethane (5 ml) until saturation was achieved. The resulting solution was allowed to stand overnight at 0°C. The solvent and excess hydrogen chloride were evaporated under reduced pressure and the residue was partitioned between ethyl acetate (19 ml) and saturated sodium bicarbonate solution (5 ml). The organic phase was separated and extracted with more saturated sodium bicarbonate solution (2 x 5 ml). The combined aqueous extracts were washed with ether (2 x 5 ml) and acidified to pH 3 with concentrated hydrochloric acid in the presence of ethyl acetate (15 ml). The acidic layer was separated and extracted with ethyl acetate (5 ml). The combined organic solutions were dried ($MgSO_4$), filtered and evaporated to give the title compound as a white solid (140 mg, 78%). Found: C,47.32; H,5.86; N,6.39. $C_{25}H_{37}N_3O_{11}S_2$. 0.75 H_2O requires C,47.71; H,6.17; N,6.68%.

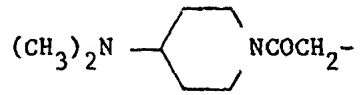
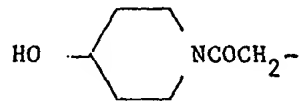
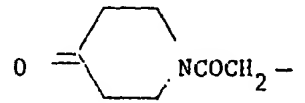
EXAMPLES 55-63

The following Examples were prepared from the corresponding t-butyl protected compounds by treatment with hydrogen chloride following the procedure given in Example 54.



Examples 55-58 and 62 are 2S isomers.

Example No	R^2-Y-	R^{16}	Form Isolated T.L.C.	Analysis (Theoretical in brackets) C	H	N
55		OH	solid 0.75 H_2O, 0.33 NH_3 Rf 0.17 (ss 3)	62.33 (64.54	7.12 6.91	8.35 7.78)
56		OH	solid 0.125 CH_2Cl_2 Rf 0.72 (ss 3)	60.15 (61.06	6.25 6.24	4.87 5.06)
57		OH	solid 0.25 CH_2Cl_2, H_2O Rf 0.59 (ss 3)	55.27 (56.94	5.99 5.84	4.57 4.70)
58		OH	White powder HCl, 0.67 H_2O Rf 0.32 (ss 3)	57.80 (57.90	6.48 6.36	7.06 7.50)

59		CH_3O-	foam H_2O, 0.25 NH_3 Rf 0.13 (ss 3)	61.75 (60.71	8.09 7.90	8.24 8.21)
60		CH_3O-	foam Rf 0.39 (ss 3)			
61		CH_3O-	foam Rf 0.48 (ss 3)	61.97 (62.13	7.08 6.82	5.82 5.75)
62	$(C_2H_5)_2NCONHCH_2$-	CH_3O-	powder Rf 0.62 (ss 3)	60.23 (61.08	7.43 7.59	8.14 8.30)
63	$(CH_3OCH_2CH_2O)_2CHCONHCH_2$-	OH	white powder Ca salt Rf 0.55 (SS 10)	53.47 (54.87	6.67 6.67	4.21 4.41)

EXAMPLE 64

N-[1-(2(S)-Carboxy-3-methoxyethoxypropyl)-1-cyclopentanecarbonyl]-O-methyl-(S)-tyrosine

An ice-cold solution of the diester from Example 28 (1.4 g) and anisol (3.0g) in dry methylene chloride (20 ml) was saturated with hydrogen chloride gas. After 30 minutes the mixture was allowed to attain room temperature and after a further 30 minutes the solvent was evaporated. The residue was chromatographed using silica gel and eluting with dichloromethane, methanol, acetic acid (95:5:0.5) to give the ethyl ester as an oil. This product was dissolved in ethanol (2 ml) and dioxane (2 ml) and hydrolysed with 1N sodium hydroxide (6 ml). After standing at room temperature for 2 hours most of the solvent was evaporated under reduced pressure, water was added, the mixture acidified with concentrated hydrochloric acid and extracted with ethyl acetate. Washing with water, drying ($MgSO_4$) and evaporation gave the title product as an oil. Rf 0.18 (ss 7). Found: C,60.45; H,7.43; N,3.36. $C_{23}H_{33}NO_8$. 0.25 H_2O requires C,60.58; H,7.40; N,3.07%.

EXAMPLE 65

N-[1-(2(R,S)-Carboxyl-10-azidodecyl)-1-cyclopentanecarbonyl]-(S)-tyrosine

The title compound was prepared from Example 27 by treatment with hydrogen chloride followed by alkaline hydrolysis following the procedure of Example 64 above; the product was obtained as a gum. Rf 0.79, (ss 3).

EXAMPLE 66

N-[1-(2(R,S)-Carboxyl-10-aminodecyl)-1-cyclopentanecarbonyl]-(S)-tyrosine

The title compound was prepared from the azido derivative of Example 65 above by hydrogenation, following the procedure given in Example 37 (part b). The product was obtained as a foam Rf 0.59, (ss 3). Found: C,64.10; H,8.49; N,4.73. $C_{26}H_{40}N_2O_6$. 0.5 H_2O requires C,64.30; H,8.51; N,5.76%.

EXAMPLE 67

N-[1-{2(S)-Carboxy-3-(4-methanesulphinylmethylbenzoylamino)-propyl}1-cyclopentanecarbonyl]-(S)tyrosine

To a cooled solution of sodium metaperiodate (39.5 mg, 0.18 mmol) in water (2 ml) was added N-[1-{2(S)-carboxy-3-(4-methyl-thiomethylbenzoylamino)propyl}-1-cyclopentanecarboxy]-(S)-tyrosine from Example 56, (87 mg, 0.16 mmol) as a solution in methanol (9 ml). Methanol was added as needed to achieve a homogeneous solution. The reaction mixture was allowed to stir at 0°C overnight. The methanol was evaporated and the aqueous residue was diluted with water (5 ml) saturated with solid sodium chloride and extracted with ethyl acetate (6 x 5 ml). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated to give the title compound as a white solid (71 mg, 80%). Found: C,57.07; H,6.26; N,4.54. $C_{28}H_{34}N_2O_8S$, 0.25 CH_2Cl_2, H_2O requires C,56.75; H,6.15; N,4.69%. Rf 0.48 (ss 3).

EXAMPLE 68

N-[1-{2(S)-Carboxy-5-{1-(4-methylpiperazinyl)}-4-methoxypentyl}-1-cyclopentanecarbonyl]-O-methyl-(S)tyrosine

a) The procedure of Example 34 was followed but using N-methylpiperazine in step (b) to give N-[1-{2(S)-(t-butoxycarbonyl)-5-{1-(4-methylpiperazinyl)}-4-methoxypentyl}-1-cyclopentanecarbonyl]-O-methyl-(S)-tyrosine t-butyl ester as a gum. Rf 0.19 (methanol, dichloromethane, acetic acid, 10:90:1). Found: C,67.01; H,9.12; N,6.42. $C_{36}H_{59}N_3O_7$ requires C,66.95; H,9.21; N,6.51%.

b) Deprotection of the above diester with trifluoroacetic acid following the procedure of Example 44, followed by ion-exchange chromatography gave the title diacid as a white powder. Rf 0.15 (ss-3). Found: C,62.68; H,8.37; N,7.76. $C_{28}H_{43}N_3O_7$ requires C,63.02; H,8.12; N,7.87%.

PREPARATION 1

3-Methoxyethoxy-2-methoxyethoxymethyl proprionic acid

a) To a solution of t-butyl 2-(bromethyl)acrylate (2.0 g, 9.00 mmol) in 2-methoxyethanol (30 ml) at room temperature was added, in one portion, potassium carbonate (2.5 g, 18 mmol) and the mixture stirred at room temperature for 72 hours. The reaction was diluted with distilled water (100 ml) and extracted with dichloromethane (100 ml). The layers were separated and the aqueous layer further extracted with dichloromethane (2 x 50 ml). The combined organic extracts were dried over magnesium sulphate, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica by eluting with ethylacetate/ hexane to give t-butyl-3-methoxyethoxy-2-methoxyethoxymethyl-propionate as a yellow oil (1.947 g, 74%), Rf 0.33 (ethyl acetate/ hexane 1:1). Found: C,57.67; H,9.85. $C_{14}H_{28}O_6$ requires C,57.51; H,9.65%

b) t-Butyl-3-methoxyethoxy-2-methoxyethoxymethylproprionate (1.60 g, 5.47 mmol) was dissolved in dichloromethane (20 ml) and cooled to 0°C. The solution was saturated with hydrogen chloride and stirred for 3 hours at 0°C. Evaporation of the solvent under reduced pressure gave the title compound as an oil (1.292 g, 100%). Found: C,49.90; H,8.41. $C_{10}H_{20}O_6 \cdot 0.07\ CH_2CH_2$ requires C,49.93; H,8.38%.

PREPARATION 2

4-(2-Iodoethoxy)-methoxybutane

a) A solution of 4-methoxybutanol (3.64 g, 34.9 mmol) in dry tetrahydrofuran (20 ml) was added dropwise under nitrogen to a stirred suspension of sodium hydride (1.05 g, 34.9 mmol, 80% dispersion in oil) in dry tetrahydrofuran (55 ml) keeping the temperature at 10°C. The resulting mixture was stirred at room temperature for 1½ hours, cooled to 10°C and 1,3,2-dioxathiolane-2,2-dioxide (4.77 g, 38.4 mmol) in dry tetrahydrofuran (30 ml) was added dropwise. After a further two hours at room temperature, water (0.63 ml, 34.9 mmol) was added followed carefully, with cooling, by concentrated sulphuric acid. After a final 1 hour stirring, solid sodium bicarbonate (7 g) was added with water (10 ml). The mixture was filtered, evaporated to a small volume without heat at reduced pressure and the residue partitioned between ethyl acetate and saturated salt solution. The organic extract on washing with brine, drying ($MgSO_4$) and evaporation gave 2-(4-methoxybutoxy)ethanol (4.54 g, 88%). Rf 0.25 (hexane, ethylacetate, 1:1). Found: C,54.98; H,10.65. $C_7H_{16}O_3 \cdot 0.25\ H_2O$ requires C,55.06; H,10.89%.

b) 4-Methylbenzenesulphonyl chloride (17.52 g, 91.90 mmol) was added to an ice cooled stirred solution of the alcohol from part a) (4.54 g, 30.63 mmol) and N-methylmorpholine (10.44 ml, 94.96 mmol) in dry methylene chloride (100 ml). After standing at 0°C for 20 hours, the solvent was evaporated under reduced pressure and the residue was chromatographed on silica eluting with increasing proportions of ethyl acetate in hexane to give the 4-methylbenzenesulphonate as an oil (6.58 g, 71%).

c) Sodium iodide (7.25 g, 48.35 mmol) was added to a stirred

solution of the above product (7.31 g, 24.17 mmol) in dimethylacetamide (30 ml), and the mixture was maintained at 60-65°C for for 20 hours. On cooling, water was added and the product extracted with ether. The organic extract was washed succesively with water, dilute sodium thiosulphate solution and water, dried ($MgSO_4$) and evaporated to give the product as an oil (5.85 g, 94%). Rf 0.45 (hexane, ethyl acetate, 1:1). Found: C,32.23; H,5.51. $C_7H_{15}IO_2$ requires C,32.56; H,5.86%.

PREPARATION 3

4-(2-Iodoethoxy)piperidine-1-carboxylic acid t-butyl ester

The title compound was prepared from 4-hydroxypyridine-1-carboxylic acid t-butyl ester following the procedure of Preparation 2 and was obtained as a clear oil. Rf 0.4 (hexane, ethyl acetate, 4:1). Found: C,40.94; H,6.20; N,3.93. $C_{12}H_{22}INO_3$ requires: C,40.58; H,6.24; N,3.94%.

PREPARATION 4

1-(2-Iodoethoxy)-4-methoxy-but-2-ene

a) Dimethyl-t-butylsilyloxyethanol (5.29 g, 30 mmol) in tetrahydrofuran (20 ml) was added dropwise under nitrogen at 10-15°C to a stirred suspension of sodium hydride (900 mg, 30 mmol, 80% dispersion in oil) in tetrahydrofuran (80 ml). On stirring at room temperature for an hour 1-bromo-4-methoxy-2-butene (5.0 g, 30 mmol) in tetrahydrofuran (20 ml) was added dropwise with ice cooling. The mixture was then stirred at room temperature overnight, cooled in ice and ether (100 ml) added, followed carefully by water (100 ml). The organic phase was

washed with water, dried ($MgSO_4$) and evaporation gave the crude product which was chromatographed on silica. Elution with a mixture of hexane and ethyl acetate (9:1) gave a pale yellow volatile oil (4.6 g, 59%).

1M Tetrabutylammonium fluoride in tetrahydrofuran (33.7 mmol) was added to a stirred ice cooled solution of the above product (4.38 g, 16.83 mmol) in tetrahydrofuran (25 ml). On stirring at room temperature overnight, ether was added and the mixture was washed with 0.5N hydrochloric acid and water. The aqueous washings were saturated with salt and extracted with ethyl acetate (3 x 100 ml). The combined organic extracts were washed with saturated salt solution, dried ($MgSO_4$) and evaporation gave a yellow oil (10.8 g). Chromatography on silica gel, eluting with a mixture of hexane and ethyl acetate (1:1) gave 2-(4-methoxy-2-butenoxy)ethanol as an oil (1.59 g, 65%). Rf 0.14 (hexane, ethyl acetate, 1:1)

b) The above product was reacted with 4-methylbenzenesulphonyl chloride followed by sodium iodide following the procedure of Preparation 1(b) to give the title compound as a pale yellow oil. Rf 0.34 (hexane, ethyl acetate, 1:1). Found: C,32.47; H,5.04. $C_7H_{13}O_2I$ requires C,32.83; H,5.12%.

PREPARATION 5

4-Chloromethoxytetrahydropyran

4-Hydroxytetrahydropyran (8.0 g, 70.33 mmol) was saturated with hydrogen chloride gas at 0°C, S-trioxane (3.24 g, 35.93 mmol) was added with stirring and hydrogen chloride introduced for a further 4 hours. The resulting solution was then diluted with a

1:1 mixture of ether and hexane (150 ml), dried over $MgSO_4$ and the solvent evaporated under reduced pressure. Distillation gave a clear oil, b.p. 100-110°C/10 torr (13.3 pa) which was used directly.

PREPARATION 6

1-(2-Iodoethoxy)-4-(dimethyl-t-butylsilyloxymethyl)benzene

a) Alpha,4-bis(Dimethyl-t-butylsilyloxy)toluene

Imidazole (49.34 g, 0.724 mmol) and dimethyl-t-butylsilyl chloride (54.62 g, 0.362 mmol) were added successively under nitrogen at 15°C to a stirred solution of 4-hydroxymethylphenol (15 g, 0.121 mmol) in dry dimethylformamide (55 ml). On stirring at room temperature for 24 hours, water was added and the mixture extracted with ether. The extract was washed with water, dried ($MgSO_4$) and evaporation gave an oil which was chromatographed on silica gel. Elution with hexane and then a mixture of ether in hexane (5:95) gave a clear oil. (36.35 g, 85%).

b) 4-(Dimethyl-t-butylsilyloxymethyl)phenol

1M Tetrabutylammonium fluoride in tetrahydrofuran (76.85 ml) was added dropwise at 0°C to a stirred solution of the product from part (a) (27.1 g, 76.8 mmol) in dry tetrahydrofuran (100 ml). After a further 30 minutes, ammonium chloride solution was added and the mixture extracted with ether. The extract was washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. Chromatography on silica gel eluting with increasing proportions of ethyl acetate in hexane gave the required product as a clear oil (4.15 g, 23%). Rf 0.4 (hexane, ethyl acetate, 4:1). Found: C,64.26; H,9.57. $C_{13}H_{22}O_2Si$, 0.25 H_2O requires C,64.28; H,9.34%.

c) 1-(2-Chloroethoxy)-4-(dimethyl-t-butylsilyloxy-methyl)benzene

Sodium hydride (515 mg, 17.6 mmol, 80% dispersion in oil) was added under nitrogen at room temperature to a stirred solution of the phenol from part (b) (4.09 g, 17.16 mmol) in dry dimethylformamide (30 ml). The mixture was heated at 60°C for 30 minutes, cooled and 2-(4-methyl-benzenesulphonyloxy)-1-chloro-ethane (3.11 ml, 17.16 mmol) added in one portion. The mixture was then reheated to 60°C for 3 hours, cooled, diluted with water and extracted with ether. The organic extract was washed with water, dried ($MgSO_4$) and solvent evaporated under reduced pressure. Chromatography on silica gel, eluting with a mixture of ethylacetate and hexane (1:9) gave the required compound as a waxy solid (2.48 g, 47%). Found: C,59.64; H,8.19. $C_{15}H_{25}ClO_2S$ requires C,59.87; H, 8.37%.

d) 1-(2-Iodoethoxy)-4-(dimethyl-t-butylsilyloxymethyl)benzene

A mixture of sodium iodide (2.44 g, 16.28 mmol) and chlorocompound from part (c) (2.45 g, 8.14 mmol) were refluxed in acetone for 3.5 days. The solvent was evaporated off and the residue partitioned between ether and water, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on silica gel, eluting with a mixture of ether and hexane (1:4) to give a clear oil (2.71 g, 85%). Rf 0.8 (ethylacetate, hexane 1:4).

PREPARATION 7

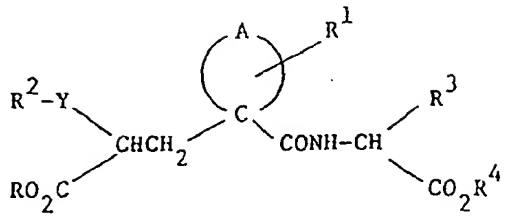
N-[1-(3-Aminopropyl-2(S)-t-butoxycarbonyl)-1-cyclopentane-carbonyl]-O-t-butyl-(S)-tyrosine-t-butyl ester

a) To an ice cold solution of 1-(2-t-butyloxycarbonyl-3-dibenzylaminopropyl)-1-cyclopentane carboxylic acid (12.7 g, 27 mmole) in dry dichloromethane (100 ml) was added 1-hydroxy-benztriazole (4.2 g, 31 mmole), and 1-ethyl-3-(dimethylamino-propyl)-carbodiimide (7 g, 36 mmole) and the resulting solution stirred at 0°C for 30 minutes. To this solution was added O-t-butyltyrosine t-butyl ester (8.4 g, 28.6 mmole) and N-methylmorpholine (5.25 g, 52 mmole) and the solution allowed to stand overnight at room temperature. The solvent was evaporated under reduced pressure and the resultant mobile oil was dissolved in methylene chloride and washed with water (2 x), 2M hydrochloric acid and saturated aqueous sodium bicarbonate (1 x) dried ($MgSO_4$), and the solution filtered and evaporated to yield the crude product as a gum. Recrystallisation from n-hexane gave N-[1-(2-t-butyloxycarbonyl-3-dibenzylaminopropyl)-1-cyclopentane-carbonyl]-O-t-butyl-(S)-tyrosine t-butyl ester as a solid (13 g, 69%), m.p. 82-87°C. A further batch of material was obtained by evaporation of the supernatant liquors and further recrystallisation. Found: C,74.12; H,8.69; N,3.87. $C_{45}H_{62}N_2O_6$ requires C,74.34; H,8.59; N,3.85%.

b) N-[1-(2-t-Butyloxycarbonyl-3-dibenzylaminopropyl)-1-cyclopentanecarbonyl]-O-t-butyl-(S)-tyrosine t-butyl ester (from part a), 19 g) was dissolved in an ethanol:water mixture (8:1, 300 ml) and hydrogenated under an atmosphere of hydrogen (60 p.s.i., 4.1 bar) at room temperature, over 20% palladium hydroxide on carbon (2 g). After 24 hours, the solution was filtered through a solkafloc pad, and the filtrate evaporated to yield an oil which crystallised. This was triturated with hexane, chilled and filtered to yield the pure enantiomer title compound as a solid (6 g, 42%) m.p. 122-127°C. Found: C,67.90: H,9.33; N,5.08. $C_{31}H_{50}N_2O_6$ requires C,68.09; H,9.22; N,5.12%.

CLAIMS

1. A compound having the formula-:



(I)

wherein:

A completes a 5 or 6 membered carbocyclic ring which may be saturated or monounsaturated;

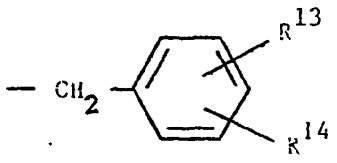
Y is an alkylene group of from 1 to 9 carbon atoms which may be straight or branched chain;

R^1 is H or (C_1-C_4)alkyl;

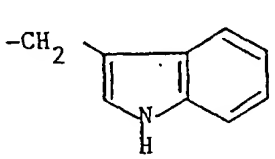
R and R^4 are each independently H, (C_1-C_6)alkyl, (C_3-C_7) cycloalkyl, benzyl, or an alternative biolabile ester-forming group;

R^2 is hydroxy, (C_1-C_6)alkoxy, hydroxy(C_2-C_6)alkoxy, (C_1-C_6)alkyl-$S(O)_n$-, (C_1-C_4)alkoxy(C_1-C_6)alkoxy, (C_1-C_4)alkyl-$S(O)_n$-(C_1-C_6)-alkoxy, (C_1-C_4)alkoxy(C_2-C_6)alkenyloxy, N_3, $(R^5)_2N$, $(R^5)_2N$-(C_1-C_6)alkoxy, $(R^5)_2N$-(C_2-C_6)alkenyloxy, heterocyclyl-Z-, heterocyclyl(C_1-C_4)alkyl-Z-, aryl-Z- or aryl(C_1-C_4)alkyl-Z, wherein Z is O, $S(O)_n$ or NR^6 and R^6 is H, (C_1-C_4)alkyl or aryl(C_1-C_4)alkyl;
or R^2 is a group of the formula R^7R^8CH- in which case Y may also be a direct link and wherein R^7 is $(R^5)_2N(C_1-C_4)$alkyl, (C_1-C_4)-alkoxy(C_2-C_4)alkylaminomethyl, heterocyclyl(C_1-C_4)alkyl or aryl and R^8 is (C_1-C_6) alkoxy, (C_1-C_4)alkoxy(C_2-C_6)alkoxy, hydroxy(C_2-C_6)alkoxy or hydroxy(C_1-C_6)alkyl;
or R^2 is a group of the formula R^9CO- wherein R^9 is a 1-piperidine or 1-piperazine group, either of which may optionally be substituted by OH, =O, (C_1-C_4)alkyl or $N(R^5)_2$;
or R^2 is a group of the formula $R^{10}CONR^6$- wherein R^6 is as previously defined, and R^{10} is $(R^6)_2N$, (C_1-C_4)alkoxy(C_2-C_4)alkyl, $R^{11}R^{12}CH$-, or substituted phenyl wherein the substituent is $(R^5)_2N$-(C_1-C_4)alkyl, (C_1-C_4)alkyl-$S(O)_n$- or (C_1-C_4)alkyl-$S(O)_n$-(C_1-C_4)alkyl;

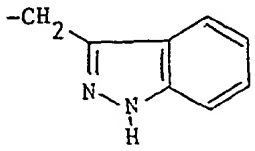
R^3 is a group of the formula:



wherein R^{13} is H, halo, 4-OH, 4-(C_1-C_6 alkoxy), 4-(C_3-C_7 cycloalkoxy), 4-(C_2-C_6 alkenyloxy), 4-[(C_1-C_6 alkoxy)carbonyloxy], 4-[(C_3-C_7 cycloalkoxy)carbonyloxy], or 3-(C_1-C_4 alkyl)SO_2NH-; and R^{14} is H, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_2-C_6) alkanoyl or halo; or R^3 is a group of the formula:



or



wherein said groups may optionally be substituted in the fused benzene ring by (C_1-C_4)alkyl, (C_1-C_4)alkoxy, OH, halo or CF_3;

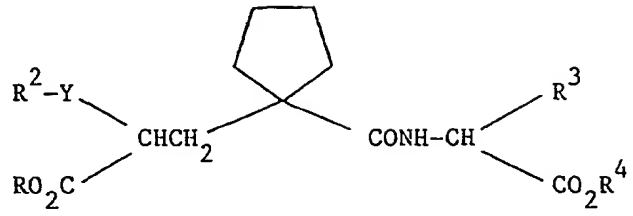
each R^5 is H, (C_1-C_6)alkyl, aryl(C_1-C_6)alkyl or the two groups R^5 are taken together to form, with the nitrogen to which they are attached, a pyrrolidinyl, piperidino, morpholino, piperazinyl or N-(C_1-C_4)alkyl-piperazinyl group;

R^{11} is (C_1-C_4)alkyl-$S(O)_n$NH- or (C_1-C_4)alkanoylamino and R^{12} is (C_1-C_4)alkyl-$S(O)_n$(C_1-C_4)alkyl or morpholinomethyl or R^{11} and R^{12} are both morpholinomethyl or (C_1-C_4)alkoxy(C_1-C_4)alkoxy(C_1-C_4)-alkyl;

n is 0, 1 or 2

or a pharmaceutically acceptable salt thereof or bioprecursor therefor.

2. A compound according to claim 1 wherein A is $(CH_2)_4$ and R^1 is H having the formula:



(II)

wherein R, R^2, R^3 and R^4 are as previously defined for formula (I).

3. A compound as claimed in claim 1 or claim 2 wherein R and R^4 are both H.

4. A compound as claimed in claim 1 or claim 2 wherein one or both of R and R^4 is a biolabile ester-forming group and said group is ethyl, indanyl, isopropyl, n-butyl, sec-butyl, t-butyl, cyclohexyl, benzyl, phenethyl, phenpropyl, acetonyl, glyceryl, pivaloyloxymethyl, 5-(4-methyl-1,3-dioxolene-2-onyl)methyl, cyclohexylmethyl, cyclohexylcarboxyethyl, cyclohexylacetoxyethyl, propionyloxyisobutyl, hexanoyloxyethyl, pentanoyloxyethyl, acetoxyethyl, acetoxybenzyl, pentanoyloxybenzyl, cyclohexyloxycarbonyloxyethyl, butyloxycarbonyloxyethyl, isobutyloxycarbonylethyl or ethoxycarbonyloxyethyl.

5. A compound as claimed in any one of claims 1 to 4 wherein R^3 is 4-hydroxybenzyl and the carbon atom to which it is attached is of (S) stereochemistry, or R^3 is 4-methoxybenzyl.

6. A compound as claimed in any one of claims 1 to 5 wherein the substituent R^2Y is (C_1-C_6)alkoxy(C_1-C_4)alkyl, (C_1-C_4)alkoxy-(C_1-C_4)alkoxy(C_1-C_6)alkyl, $H_2N(C_4-C_9)$alkyl, or $R^{10}CONHCH_2-$ wherein R^{10} is substituted phenyl and said substituents are as previously defined in claim 1.

7. A compound according to claim 1 wherein said compound is:

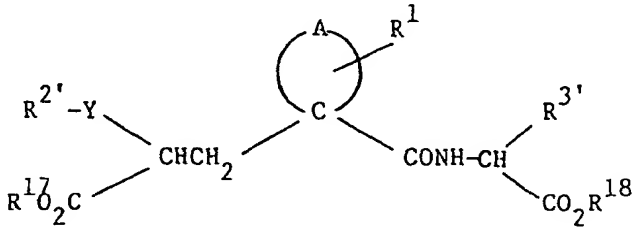
N-[1-{2(S)-carboxy-4-(2-methoxyethoxy)pentyl}-1-cyclopentane-carbonyl]-(S)-tyrosine,

N-[1-(2(S)-carboxy-4-ethoxy-butyl)-1-cyclopentanecarbonyl]-(S)-tyrosine,

N-[1-(2(R,S)-carboxy-10-aminodecyl)-1-cyclopentanecarbonyl]-(S)-tyrosine and

N-[1-{2(S)-carboxy-3-(4-aminomethylbenzamido)propyl}-1-cyclo-pentanecarbonyl]-(S)-tyrosine.

8. A process for preparing a compound of the formula (I) as defined in claim 1 which comprises subjecting a compound of the formula:



(V)

wherein A, Y and R^1 are as previously defined, $R^{2'}$ and $R^{3'}$ are as defined for R^2 and R^3 with any reactive groups therein protected if necessary and R^{17} and R^{18} are as defined for R and R^4 excluding H, or they are conventional carboxylic acid protecting groups; to a hydrolysis and/or hydrogenation and/or other deprotection reaction to remove any protecting group present in $R^{2'}$ or $R^{3'}$, and

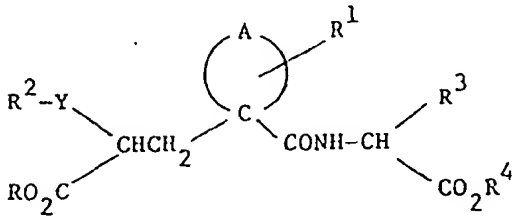
either to remove both of R^{17} and R^{18} to yield the corresponding dicarboxylic acid wherein R and R^4 are both H or to remove one of R^{17} and R^{18} to yield the corresponding mono-ester product wherein one of R and R^4 is H and the other is a biolabile ester-forming group; and optionally forming a pharmaceutically acceptable salt of the product;

9. A pharmaceutical composition comprising a compound of the formula (I) or (II) as claimed in any of claims 1 to 7 or a pharmaceutically acceptable salt thereof or bioprecursor therefor, together with a pharmaceutically acceptable diluent or carrier.

10. A compound of the formula (I) or (II) as claimed in any of claims 1 to 7 or a pharmaceutically acceptable salt thereof or bioprecursor therefor, for use in medicine, particularly for the treatment of hypertension, heart failure, renal insufficiency, angina, premenstrual syndrome, cyclical oedema, Menieres disease, hyperaldosteroneism (primary and secondary) hypercalciuria, glaucoma, asthma, inflammation, pain, epilepsy, affective disorders, dementia and geriatric confusion, obesity and gastrointestinal disorders (especially diarrhoea and irritable bowel syndrome), the modulation of gastric acid secretion or the treatment of hyperreninaemia.

PROCESS CLAIMS

1. A process for preparing a compound having the formula-:



(I)

wherein:

A completes a 5 or 6 membered carbocyclic ring which may be saturated or monounsaturated;

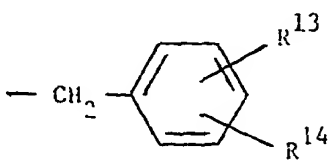
Y is an alkylene group of from 1 to 9 carbon atoms which may be straight or branched chain;

R^1 is H or (C_1-C_4)alkyl;

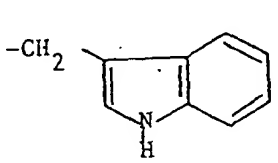
R and R^4 are each independently H, (C_1-C_6)alkyl, (C_3-C_7) cycloalkyl, benzyl, or an alternative biolabile ester-forming group;

R^2 is hydroxy, (C_1-C_6)alkoxy, hydroxy(C_2-C_6)alkoxy, (C_1-C_6)alkyl-$S(O)_n$-, (C_1-C_4)alkoxy(C_1-C_6)alkoxy, (C_1-C_4)alkyl-$S(O)_n$-(C_1-C_6)-alkoxy, (C_1-C_4)alkoxy(C_2-C_6)alkenyloxy, N_3, $(R^5)_2N$, $(R^5)_2N$-(C_1-C_6)alkoxy, $(R^5)_2N$-(C_2-C_6)alkenyloxy, heterocyclyl-Z-, heterocyclyl(C_1-C_4)alkyl-Z-, aryl-Z- or aryl(C_1-C_4)alkyl-Z, wherein Z is O, $S(O)_n$ or NR^6 and R^6 is H, (C_1-C_4)alkyl or aryl(C_1-C_4)alkyl;
or R^2 is a group of the formula R^7R^8CH- in which case Y may also be a direct link and wherein R^7 is $(R^5)_2N(C_1-C_4)$alkyl, (C_1-C_4)-alkoxy(C_2-C_4)alkylaminomethyl, heterocyclyl(C_1-C_4)alkyl or aryl and R^8 is (C_1-C_6) alkoxy, (C_1-C_4)alkoxy(C_2-C_6)alkoxy, hydroxy(C_2-C_6)alkoxy or hydroxy(C_1-C_6)alkyl;
or R^2 is a group of the formula R^9CO- wherein R^9 is a 1-piperidine or 1-piperazine group, either of which may optionally be substituted by OH, =O, (C_1-C_4)alkyl or $N(R^5)_2$;
or R^2 is a group of the formula $R^{10}CONR^6$- wherein R^6 is as previously defined, and R^{10} is $(R^6)_2N$, (C_1-C_4)alkoxy(C_2-C_4)alkyl, $R^{11}R^{12}CH$-, or substituted phenyl wherein the substituent is $(R^5)_2N$-(C_1-C_4)alkyl, (C_1-C_4)alkyl-$S(O)_n$- or (C_1-C_4)alkyl-$S(O)_n$-(C_1-C_4)alkyl;

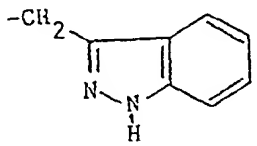
R^3 is a group of the formula:



wherein R^{13} is H, halo, 4-OH, 4-(C_1-C_6 alkoxy), 4-(C_3-C_7 cycloalkoxy), 4-(C_2-C_6 alkenyloxy), 4-[(C_1-C_6 alkoxy)carbonyloxy], 4-[(C_3-C_7 cycloalkoxy)carbonyloxy], or 3-(C_1-C_4 alkyl)SO_2NH-; and R^{14} is H, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_2-C_6) alkanoyl or halo; or R^3 is a group of the formula:



or



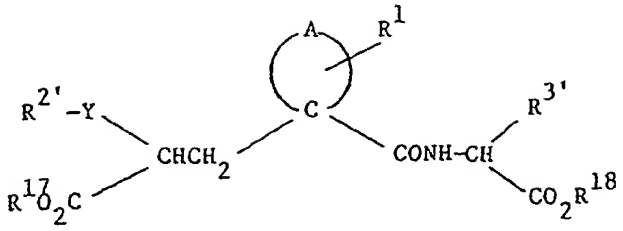
wherein said groups may optionally be substituted in the fused benzene ring by (C_1-C_4)alkyl, (C_1-C_4)alkoxy, OH, halo or CF_3;

each R^5 is H, (C_1-C_6)alkyl, aryl(C_1-C_6)alkyl or the two groups R^5 are taken together to form, with the nitrogen to which they are attached, a pyrrolidinyl, piperidino, morpholino, piperazinyl or N-(C_1-C_4)alkyl-piperazinyl group;

R^{11} is (C_1-C_4)alkyl-$S(O)_n$NH- or (C_1-C_4)alkanoylamino and R^{12} is (C_1-C_4)alkyl-$S(O)_n$(C_1-C_4)alkyl or morpholinomethyl or R^{11} and R^{12} are both morpholinomethyl or (C_1-C_4)alkoxy(C_1-C_4)alkoxy(C_1-C_4)-alkyl;

n is 0, 1 or 2

or a pharmaceutically acceptable salt thereof or bioprecursor therefor; which comprises subjecting a compound of the formula:



(V)

wherein A, Y and R^1 are as previously defined, $R^{2'}$ and $R^{3'}$ are as defined for R^2 and R^3 with any reactive groups therein protected if necessary and R^{17} and R^{18} are as defined for R and R^4 excluding H, or they are conventional carboxylic acid protecting groups; to a hydrolysis and/or hydrogenation and/or other deprotection reaction to remove any protecting group present in $R^{2'}$ or $R^{3'}$, and either to remove both of R^{17} and R^{18} to yield the corresponding dicarboxylic acid wherein R and R^4 are both H or to remove one of R^{17} and R^{18} to yield the corresponding mono-ester product wherein one of R and R^4 is H and the other is a biolabile ester-forming group; and optionally a pharmaceutically acceptable salt of the product;

2. A process according to claim 1 wherein R^{17} is t-butyl and R^{18} is t-butyl and said groups are removed by treatment with anhydrous trifluoroacetic acid or hydrogen chloride to yield the corresponding dicarboxylic acid of formula (I) wherein R and R^4 are both H.

3. A process according to claim 1 wherein R^{17} is t-butyl and R^{18} is (C_1-C_6)alkyl and said groups are removed by treatment with anhydrous trifluoroacetic acid or hydrogen chloride followed by hydrolysis with aqueous alkali to yield the corresponding dicarboxylic acid of formula (I) when R and R^4 are both H.

4. A process according to claim 1 wherein R^3 is 4-hydroxybenzyl and the carbon atom to which it is attached is of (S) stereochemistry, or R^3 is 4-methoxybenzyl.

5. A process according to claim 1 wherein the substituent R^2Y is (C_1-C_6)alkoxy(C_1-C_4)alkyl, (C_1-C_4)alkoxy(C_1-C_6)alkoxy-(C_1-C_4)alkyl, $H_2N-(C_4-C_9)$alkyl or $R^{10}CONHCH_2-$ wherein R^{10} is subsituted phenyl and said subsituents are as previously defined in claim 1.

6. A process as claimed in claim 1 wherein the compound of formula (I) produced is-:

N-[1-{2(S)-carboxy-4-(2-methoxyethoxy)pentyl}-1-cyclopentane-carbonyl]-(S)-tyrosine,

N-[1-(2(S)-carboxy-4-ethoxybutyl)-1-cyclopentanecarbonyl]-(S)-tyrosine,

N-[1-(2(R,S)-carboxy-10-aminodecyl)-1-cyclopentanecarbonyl]-(S)-tyrosine and

N-[1-{2(S)-carboxy-3-(4-aminomethylbenzamido)propyl}-1-cyclo-pentanecarbonyl]-(S)-tyrosine.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 91/00296

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[5]: C 07 C 237/24, A 61 K 31/16, C 07 C 271/22, 323/60, 235/40, C 07 D 309/12, C 07 D 211/46, C 07 C 247/12, C 07 D 295/145, ./.

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[5]	C 07 C 237/00, 235/00, 233/00, 311/00, 323/00, C 07 D 211/00, 295/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	GB, A, 2218983 (PFIZER) 29 November 1989 see examples; claims --	1-10
A	EP, A, 0343911 (PFIZER) 29 November 1989 see examples; claims --	1-10
A	EP, A, 0274234 (PFIZER) 13 July 1988 see examples; claims cited in the application --	1-10
P,X	EP, A, 0358398 (PFIZER) 14 March 1990 see examples 57-59,61,63-76,78,79,81; claims cited in the application ----------	1-5,8-10

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
23rd May 1991	12. 07. 91
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	N. Toribio Nuria TORIBIO

Form PCT/ISA/210 (second sheet) (January 1985)